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UDO JULIUS WILE, M.D.

Dedication

THIS VOLUME is dedicated to Dr. Udo Julius Wile, who organized the first three year training course for dermatosyphilologists in an American university, who served with distinction in World Wars I and II, who has contributed many articles of a fundamental and original type to the dermatologic and syphilologic literature and who has trained numerous men in this field, many of whom have attained professional rank in some of the leading medical colleges of this country. The contributors to this volume are all former undergraduate or postgraduate students of Dr. Wile's. Although he retired on Aug. 8, 1948 as director of the department he founded, it is hoped that he will continue his professional and recreational activities for many years to come.

EDITORIAL BOARD.

Archives of Dermatology and Syphilology

VOLUME 60 AUGUST 1949 NUMBER 2

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TRIBUTE TO DR. UDO JULIUS WILE

ARTHUR C. CURTIS, M.D.
AND
EDWARD P. CAWLEY, M.D.
ANN ARBOR, MICH.

IN THE estimation of his colleagues, Dr. Udo J. Wile has attained international renown as a dermatologist and syphilologist. To this man's extraordinary talent as a student, teacher and clinician is directed this appreciation, to commemorate his retirement from formal academic pursuits, Aug. 8, 1947.

Dr. Wile was born in New York on Aug. 8, 1882. Having been granted his academic degree by Columbia University in 1904, he attended Johns Hopkins University School of Medicine and was graduated three years later. On completion of his second year in medical school he devoted his summer vacation to the study of pathology under guidance of the eminent internist Harlow Brooks, performing more than one hundred necropsies. Dr. Wile's special interest in syphilology was conceived during his internship. After routine days at Sydenham Hospital, he devoted evenings to the operation of a venereal disease clinic at the Hudson Street Hospital for Dr. Victor Peterson, being host on several occasions to Drs. Simon Flexner and Hideyo Noguchi and furnishing them with fresh material for their first attempts to culture the Treponema pallidum.

When he decided to make cutaneous medicine and syphilology his field of special endeavor, Dr. Wile sailed for Europe to pursue his studies in the winter of 1907. Because the illustrious Prof. J. Jadassohn was absent on a prolonged holiday, Dr. Wile spent only a month in this famous clinic at Berne, Switzerland. He next traveled to the University of Berlin, Germany, where he became a graduate student and subsequently an assistant in Lesser's clinic at the Charité hospital. During his tutelage in Berlin he carried out investigations in Schaudinn's laboratory, working with Erich Hoffman. He also became a close friend of Andre Civatte, himself a visiting graduate student from Paris, France, and in collaboration with Franz Blumenthal, then a clinic assistant, published a sound discourse concerned with the complement fixation test in the urine of syphilitic persons. A letter from Albert Neisser awarding him membership in the German Dermatological Society climaxed a highly profitable year in Berlin.

During his stay in Berlin and in Paris, to which he traveled next, Dr. Wile was the only American physician devoting himself to the field of dermatology and syphilology. His Parisian teachers, acquaintances and associates of the time comprise in retrospect a scintillating array of preeminent personages in the speciality. Through the influence of his friend Civatte he became a student of Darier at the Hôpital Broca, where he spent three afternoons each week with the old master. The remainder of his energies were divided between Brocq's service at the Hôpital St. Louis, the École Lallier, conducted by Sabouraud and devoted exclusively to the care of children with ringworm of the scalp, and the celebrated Baretta museum which contained an astounding store of teaching moulages. Pautrier, Brocq's intern at the time, and Dr. Wile have maintained through the years a close and abiding friendship. Other French contemporaries of the day with whom Dr. Wile has continued a lasting friendship are Paul Ravaut, Clement Simon, Levy-Bing and Pierre Fernet. From Ravaut, then Thiebierge's assistant at the Hôpital St. Louis and a pioneer in the field of neurosyphilis, he acquired a special interest in this variant of the disease, and learned the technic of lumbar puncture as well as sound interpretation of the findings.

After a year in Paris Dr. Wile, now an enthusiastic dermatologist and syphilologist, proceeded to the Dermatologicum in Hamburg, Germany. Pollitzer, Norman Walker, Schamberg, Engman Sr. and Haase had preceded him at this private clinic maintained by Unna. During his three months' tenure he applied himself to an intensive study of dermatopathology and carried out as well an original piece of work on microchemistry of the skin. Unna's deep regard for Dr. Wile was expressed a few months later when he designated him corresponding editor of the *Dermatologische Wochenschrift.*

Bearing an introductory letter from his former teacher, Sir William Osler, Dr. Wile proceeded next to London for three months. Radcliffe Crocker's Clinic and St. Thomas Hospital served as his headquarters, though he also spent time with Sequiera at the London Hospital and met on several occasions with Sir Norman Walker. Utilizing a dark field device acquired in Berlin, he accomplished for the edification of Graham Little's students at St. Mary's Hospital, and for the first time in the British Isles, the demonstration of the living T. pallidum. Also during his stay he presented to Sir Jonathan Hutchinson specimens of the original microscopic sections of silver-stained tissue from patients with congenital syphilis, in which spirochetes could be seen.

return to New York a position with Sigmund Pollitzer as instructor in return to New York a poistion with Sigmund Pollitzer as instructor in dermatology and syphilology at the Post-Graduate Medical School and Hospital and as his assistant at the Lenox Hill Hospital. At the same time he maintained a private office in the Sydenham Building for practice

of his speciality. In 1909 he became an assistant at the New York Skin and Cancer Hospital under George H. Fox, serving with MacMurtry, Wise and Howard Fox as contemporaries.

In 1912 the chair of dermatology and syphilology at the University of Michigan Medical School was vacant, and Dr. Wile was appointed to the position on the recommendation of Dr. Rufus Cole of the Rockefeller Institute.

The entrance of the United States into hostilities of World War I curtailed temporarily his academic career. As a reserve medical officer he reported for active duty May 25, 1917, and in July 1917 he reached Liverpool, England, despite the enemy-engineered sinking of his transport in the Hudson River. Subsequently he served in Paris and in a base hospital on the river Meuse. He was later transferred to England, where he organized and was instrumental in the construction at Liverpool of American Military Hospital 4, of which he was commanding officer. This organization was the initial American military establishment in Great Britain.

Having established the first university hospital clinic for training of dermatologists and syphilologists in the United States, Dr. Wile returned after the war to Ann Arbor, Mich., and continued direction of a vigorous and exceptionally productive program in his field of specialization, a program which has probably not been excelled on this continent as a polific source of well trained dermatologists. Among the graduates of his staff are numbered such eminent physicians as John H. Stokes, Francis E. Senear, Lyle B. Kingery, Carroll S. Wright and George H. Belote. His bibliography consists of one hundred and forty-five papers, which throughout the years have been pertinent, informative and masterfully written, and which have concerned themselves with a varied array of topics in the fields of both dermatology and syphilology. Demonstration of the transmissibility of the causative agent of warts and molluscum contagiosum, endocrine determinations in acne vulgaris and fundamental studies concerned with the interrelationship of lymphoblastomas with certain varieties of parapsoriasis are a few of the dermatologic subjects illuminated by his writings. Dr. Wile's authorative monographs on visceral syphilis and the "therapeutic paradox" have become widely quoted sources of information, and his pioneer work concerned with an infravisible form of T. pallidum has received general acclaim. He called attention to the tabetic habitus and pointed out a number of years ago the frequent extension, in persons with congenital syphilis, of the labial epithelium to involve the mucous membrane, the latter manifestation being frequently referred to as Wile's sign. Such scattered commentaries, however, give but little of the wealth of information contained in his numerous contributions to the literature.

Dr. Wile accepted an appointment in 1926 to the advisory staff of the Surgeon General of the United States Public Health Service. Shortly thereafter, together with Drs. Moore, Stokes, Cole and O'Leary, he participated in the well known activities and outstanding publications on syphilis of the Cooperative Group.[1] In 1912 he was commissioned medical director in the same branch of service and, again taking temporary leave of his university affiliations, embarked on a tour of active duty. He was instrumental in locating and establishing sixty-two rapid treatment centers at various strategic areas throughout the United States; Dr. Wile served simultaneously in the capacity of chief medical consultant to these institutions, which had as their objective the minimization of a war-born increase in venereal disease. The remarkable results attained by these units are appropriate testimony to his skill both as an administrator and as a syphilologist. On reaching the mandatory retirement age of 64, Dr. Wile was promptly reengaged as special consultant to the United States Public Health Service, a position which he continues to hold.

Dr. Wile has been elected at various times to most of the distinguished dermatologic societies of the world, including presidency of the American Dermatological Association in 1929-1930, as well as vice presidency of the International Congress of Dermatology and Syphilology in Copenhagen, Denmark, in 1930. At the request of the French government in 1946, Dr. Wile was sent to France to initiate that country's penicillin program in the treatment of venereal disease. At the conclusion of this assignment he was made honorary member of the French Society of Dermatology and Syphilography. At the same time he received from the French government the medal and citation as *Commandeur de l'Ordre de la Santé Publique,* the highest of four ranks in an honorary organization, the upper brackets of which have seldom included an American physician.

Though retiring from further arduous academic duties, Dr. Wile's intellectual integrity, his capabilities as a vigorous and earnest teacher, his astounding diagnostic acumen and his lofty character have stamped him for all time as one of the great men of dermatology.

University of Michigan Medical School, Ann Arbor, Mich.

1. Group for Cooperative Studies in the Treatment of Syphilis.

ERYTHEMA MULTIFORME FOLLOWING HIGH VOLTAGE ROENTGEN THERAPY

Review of the Literature and Report of Three Cases

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HONOLULU, HAWAII

GUIDO HOLZKNECHT [1] reported in 1903, from Löw's Sanatorium in Vienna, 5 cases of a generalized febrile illness associated with roentgen dermatitis. The first patient, a 50 year old woman irradiated for facial hirsutism, had fever and an "erythema" limited to the neck and upper portion of the trunk, in association with a moderately severe roentgen dermatitis of the irradiated areas. Case 2 consisted of a universal papular eruption, with fever, in an 8 year old boy irradiated for psoriasis of the scalp. The third case was that of a 20 year old girl, irradiated for facial hirsutism, who acquired a scarlatiniform eruption with fever. Case 4 occurred in a 5 year old boy with favus of the scalp and consisted of fever and a pruritic, generalized exanthem of small papules, with vesicles in some areas. The fifth case was that of a 50 year old woman with psoriasis, who exhibited fever without any exanthem after roentgen therapy. The eruption in all cases began from ten days to four weeks after the roentgen treatment, which was generally given in a single sitting; it was associated with a moderately severe roentgen dermatitis in the irradiated area, and it had a benign course terminating in spontaneous recovery within a few days to a few weeks.

Holzknecht attributed this reaction to absorption of toxic substances from the irradiated tissues. He concluded, "One occasionally observes, at the height of a severe or widespread roentgen reaction, a toxemic symptom-complex consisting of high fever with generalized illness, with or without an exanthem, and with an excellent prognosis."

Schreiner,[2] in 1923, seems to have been the next to report an instance of this unusual reaction. His case was one of generalized

From the Department of Dermatology of the Clinic.

1. Holzknecht, G.: Fieberhafte Allgemeinerkrankung mit Exanthem bei Röntgendermatitis, Arch. f. dermat. u. syph. **66**:71, 1903.

2. Schreiner, K.: Rezidivierendes Röntgenexanthem, Strahlentherapie **16**:389, 1924; cited by Reisner and Brada.[6]

lichen ruber planus developing on the twelfth day after irradiation of the thymus, which reaction subsequently recurred after irradiation of the lumbar region. In 1925 Bloch [3] reported the case of a patient, irradiated for carcinoma of the uterus on February 25 and March 2, who exhibited fever on March 13, had an eczematoid exanthem on March 28, and, after having made a complete recovery by April 18, had a relapse on May 3, with a universal exfoliative dermatitis. Despite subsequent complication by severe pyoderma, the patient made a complete recovery under treatment with intravenous injections of sodium thiosulfate and nonspecific topical applications *(indifferenter Lokalbehandlung)*. Epstein,[4] in 1926, reported an instance of a purpuric exanthem in a patient being irradiated for uterine carcinoma.

After this flurry of interest, no further publications appear to have been made until Berenstein,[5] in 1932, reported from the Institut für Mutter-und Kinderschutz, in Kiew, that he had observed several instances of a confluent, erythematous, scarlatiniform eruption, associated with slight fever and pronounced eosinophilia (15 to 19 per cent), on the neck, shoulders, chest and inner aspects of the arms and legs of children who had undergone roentgen epilation of the scalp from three to five weeks before. The eruption in all cases healed in from two to four weeks under bland treatment.

A conservative note was sounded in the following year, 1933, by Reisner and Brada,[6] of the University Institute for Radiation Therapy in Frankfort on the Main. They called attention to the fact that such generalized eruptions as had been described as following localized radiation therapy might occur spontaneously and might be elicited by drugs and also that the experience of most observers was that such eruptions were extremely rare; indeed, they had not observed a single example of them. They expressed the belief that, though these eruptions might occur after roentgen irradiation, they did not occur because of *(durch)* roentgen irradiation.

Pardo Castelló [7] reported from Habana, in 1936, 4 cases of what he designated conservatively (cf. Reisner and Brada) "allergic gen-

3. Bloch, B.: Universelle Dermatitis nach Bestrahlung eines Carc. uteri, Schweiz. med. Wchnschr. **55**:744, 1925.

4. Epstein, P.: Severe General Vascular Injuries Simulating Werlhof's Disease Following Intensive Local Roentgen Ray Treatment, Strahlentherapie **21**:416, 1926; cited by Reisner and Brada.[6]

5. Berenstein, B. M.: Generalisierte Exantheme nach Röntgenbestrahlung, Röntgenpraxis (No. 23) **4**:1014, 1932.

6. Reisner, A., and Brada, H.: Generalisierte Exantheme durch Röntgenbestrahlung, Röntgenpraxis **5**:16, 1933.

7. Pardo Castelló, V.: Allergic Cutaneous Eruptions After High Voltage Roentgen Therapy, Arch. Dermat. & Syph. **33**:886 (May) 1936.

eralized cutaneous eruptions *after* high voltage roentgen therapy." Two of these were morbilliform, one merely erythematous and one varicelliform. All had a benign course, clearing within from five to twenty days.

But the disease was evidently a rare one, and its literature was still comparatively obscure. In 1941, H. H. Hopkins [8] reported from Baltimore the case of a patient who was given, after mastectomy for carcinoma, approximately 2,000 r of high voltage roentgen rays to each of three ports over a period of twenty days. She presented a reaction (erythema and edema) in the irradiated areas, followed by diffuse generalized erythema and purpura, which spared only the face and was associated with fever, tachycardia, pains in the joints, general prostration and relative leukopenia (5,000 to 7,000 leukocytes per cubic millimeter). The result of the tourniquet test was positive. Platelets were not diminished in the blood. The urine was normal. Sulfanilamide was given, and the patient recovered. The case was interpreted as an instance of acute disseminated lupus erythematosus precipitated by roentgen therapy and cured by sulfanilamide. The evidence was equivocal, however, and would seem to have justified equally well a diagnosis of erythema multiforme following high voltage roentgen therapy. That this possibility occurred to Hopkins is apparent from his statement that "such a generalized reaction to local radiation has never been reported."

Later in the same year (1941) Castigliano [9] published an excellent review of the whole subject entitled "Dermatoses Associated with Roentgen Therapy," with an extensive bibliography and a report of 5 cases. All his cases, however, were examples of infectious eczematoid dermatitis, so called, confined to the irradiated area and the adjacent skin; they began from one to twelve weeks after irradiation, and they required considerable specific local treatment for their relief. Castigliano concluded that this type of reaction was by far the commonest dermatosis associated with roentgen therapy, and he reiterated Reisner's warning against the error of attributing eruptions due to drugs to roentgen irradiation.

It would seem, then, that at least two types of cutaneous reaction to roentgen irradiation, in addition to the primary reaction to irradia-

8. Hopkins, H. H.: Acute Disseminated Lupus Erythematosus: Precipitation by Roentgen Rays and Cure with Sulfanilamide, Arch. Dermat. & Syph. **43**:833 (May) 1941.

9. Castigliano, S. G.: Dermatoses Associated with Roentgen Therapy, Am. J. Roentgenol. **46**:518, 1941.

tion which is familiar to the roentgenologist who administers high voltage roentgen therapy, may occur: a relatively common localized form, which may be called infectious eczematoid dermatitis, and a relatively rare generalized form, which seems best classified simply as erythema multiforme. The latter form may, of course, be caused

Fig. 1 (case 1).—Erythematous and pigmented macules in sites of healed bullae, a week after the patient's discharge from the hospital, the distribution and severity of the eruption being evident.

by drugs, and it may therefore be difficult or even impossible for one to be sure whether it has been caused by irradiation or not. If it is due to irradiation, Holzknecht's original explanation—that it results from absorption of toxic materials from the irradiated tissues—seems most reasonable.

Because of the evident rarity of this syndrome, which has made it generally unfamiliar to dermatologists and roentgenologists alike, the following cases are reported.

REPORT OF CASES

CASE 1.—C. I., a 29 year old Chinese man, was first seen by me on Feb. 10, 1947, because of classic generalized erythema multiforme bullosum of three days' duration, with beautiful iris lesions, moderately severe involvement of the mucous membrane and a temperature of 101 F. He gave a history of having received

Fig. 2 (case 1).—The patient's thigh, with confluence of lesions and a stippled pattern of scar formation in the involved areas.

high voltage roentgen therapy, and it was learned that between Nov. 15, 1946, and Feb. 6, 1947, he had received almost 12,000 r, divided over seven ports, directed at abdominal metastases from a seminoma of the right testicle which had been excised on Nov. 1, 1946. Both the patient and his family positively denied that he had needed or taken any medication whatever for at least three weeks, if not longer; his roentgenologist confirmed this statement so far as his knowledge went.

He was admitted to Queen's Hospital and given the following treatment: tub baths in a solution of potassium permanganate (1:6,000); diphenhydramine (benadryl®) hydrochloride orally, 50 mg. every four hours; 100 mg. of ascorbic acid

four times daily, and calcium gluconate given intravenously, 1 Gm. daily. Petrolatum gauze dressings were applied to the lips and petrolatum gauze pressure dressings to the extremities, and penicillin was given intramuscularly, 20,000 units every three hours. After the initial progression of the large bullous lesions, improvement began, and in just two weeks, on February 25, the eruption had healed sufficiently to permit the patient to be discharged from the hospital without dressings.

On March 13, the diagnosis of abdominal lymphatic metastases was confirmed during a laparotomy for acute appendicitis, and on May 26 the patient died of neoplastic disease, without having had a recurrence of any cutaneous lesions. Autopsy was not performed.

CASE 2.—E. K., a 58 year old Japanese housewife, was seen on April 19, 1947, because of deep red, patchy erythema of the palms and soles, which had been present for three days, associated with moderately severe pruritus and a generalized, indistinct, moderately pruritic, erythematous papular eruption. Between Feb. 10 and April 4, 1947, she had received 2,000 r of filtered high voltage roentgen rays to each of four areas for an extensive, inoperable, anaplastic carcinoma arising in the urethra.

Ascorbic acid, 100 mg. three times daily, was prescribed, together with diphenhydramine hydrochloride, 50 mg. three times daily and, for local use, 0.5 per cent menthol in equal parts of 95 per cent alcohol and ether. Two weeks later the itching had almost stopped and the erythema was much diminished, though there was a surprising degree of thickening of the palms and soles, suggesting the keratotic "sandal" pattern of pityriasis rubra pilaris. Within two more weeks, however, complete clearing had occurred.

CASE 3.—E. T., a 51 year old housewife of Caucasian parentage, was seen on Jan. 27, 1947, with a profuse eruption of deep-seated papules the color of normal skin, 2 to 6 mm. in diameter, on the external aspects of both arms. There was no associated itching or other discomfort. Between Dec. 11, 1946 and Jan. 21, 1947 she had received 2,000 r of filtered high voltage roentgen rays to each of three ports after radical mastectomy for carcinoma of the left breast.

Ascorbic acid, 100 mg., three times a day, was prescribed. The papules gradually became somewhat erythematous, but they slowly decreased in size, and the eruption faded entirely over a period of two or three weeks.

COMMENT

It seems probable that the eruption in case 1 was caused by the roentgen irradiation. The whole picture fits in very well with that of the eruptions described by Holzknecht,[1] Bloch,[3] Berenstein,[5] Pardo Castelló[7] and Hopkins.[8] It is true that bullous erythema multiforme may occur in an apparently healthy person without discoverable cause and that its occurrence in this patient during irradiation could be purely coincidental; still, the dose was large, the irradiated area was extensive, and the likelihood of absorption of potentially toxic or allergenic substances from the heavily irradiated tissues cannot be denied. The usual method of proof—reproduction of the same reaction by a second exhibition of the suspected cause—is inapplicable here for obvious reasons.

The eruptions in cases 2 and 3, while unusual in their appearance and benign in their course and consistent with the picture of a reaction to an internally acting allergen, were not so clearly attributable to irradiation. They are included here merely as possible examples of this phenomenon, for comparison with similar cases which may be reported in the future.

SUMMARY AND CONCLUSIONS

Holzknecht appears to have been the first to describe an erythema multiforme–like reaction following intensive high voltage roentgen therapy.

It appears that this is a relatively rare allergic manifestation and that it may be attributed to the irradiation (though proof is rarely possible) if an eruption due to drugs can be excluded with reasonable certainty.

The disorder seems to run a benign course in almost all instances, the most serious eventuality being the development of exfoliative dermatitis.

Antihistaminic drugs may be of some value in treatment, but in general supportive measures are probably more important.

The Clinic, 881 South Hotel Street.

TREATMENT OF EARLY SYPHILIS WITH PENICILLIN

Report on Three Hundred and Twenty-Four Patients Treated with 1,200,000 Units Over Seven and One-Half Days

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CINCINNATI

THE PUBLICATION of a report by Mahoney, Arnold and Harris.[1] in 1943 on the effectiveness of 1,200,000 units of penicillin given over an eight day period stirred the world of syphilotherapy profoundly. It was not long before other investigators published their results of treatment in early syphilis with similar amounts of the drug. Thus, Binkley and Kile [2] reported their observation on 10 patients, who had received 1,200,000 units of penicillin over varying periods of time, 7 of whom were seronegative and clinically well one year after treatment. In a recent article by the Committee on Medical Research of the Office of Scientific Research and Development and the United States Public Health Service [3] the results of treatment were given in 1,073 patients with early syphilis; 1,200,000 units of penicillin were used over a seven and one-half day period in intramuscular injections given every three

---

Under the direction of Herman N. Bundesen, Senior Surgeon (R) United States Public Health Service (Inactive), President, Chicago Board of Health.

From the Chicago Intensive Treatment Center, Venereal Disease Control Program, Chicago Board of Health, in cooperation with the United States Public Health Service.

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the office of Scientific Research and Development and the Chicago Intensive Treatment Center.

1. Mahoney, J. F.; Arnold, R. C., and Harris, A.: Penicillin Treatment of Early Syphilis: Preliminary Report, Am. J. Pub. Health **33**:1387, 1943.

2. Binkley, G. W., and Kile, R. L.: Rapid Treatment of Early Syphilis with Small Doses of Penicillin: Observations in One Hundred and Fifty-Nine Cases, Arch. Dermat. & Syph. **51**:200 (March) 1945.

3. Penicillin in Early Syphilis, Committee on Medical Research and the U. S. Public Health Service, J. A. M. A. **131**:265 (May 25) 1946.

hours. Of these, however, only 35.2 per cent were followed for from two hundred and eighty-one to three hundred and eight days. Patients followed for eleven months presented a cumulative failure rate of 18 per cent.

As one of the member clinics of the Subcommittee on Venereal Diseases of the National Research Council, the Chicago Intensive Treatment Center participated in the concerted attempt to delineate the optimal time-dose relationship of aqueous sodium penicillin administered intramuscularly in early syphilis. It had previously been ascertained that amounts of penicillin smaller than 1,200,000 units given over a seven and one-half day period were inadequate in the treatment of early syphilis.[4] It had also been established that 1,200,000 units given over a three and three-quarter day period likewise constituted unsatisfactory treatment.[5]

Accordingly, under a grant from the National Research Council, an investigative study was launched in December 1944 for the purpose of determining the efficacy of a schedule of treatment in which an aqueous solution of sodium penicillin was administered intramuscularly every three hours, 20,000 units per injection for a total of sixty injections, or 1,200,000 units of penicillin. The period of treatment extended over seven and one-half days.

For this study, 324 patients with dark field positive syphilis were treated by the above schedule of treatment from December 1 through July 23, 1945. No further treatment was administered unless either clinical or serologic relapse occurred or pregnancy intervened. Results of observation of these patients over a maximum period of twenty-three months and a minimum of sixteen months are presented.

The distribution of these patients by race, sex and age is indicated in table 1. The age of the patients ranged from 8 to 48 years; 19.4 per cent were under 20 years, 35.5 per cent were 20 to 24 years and 45.1 per cent 25 years and over. The distribution according to the stage of syphilis is given in table 2.

Of the entire group, 257 patients had received no previous treatment for syphilis. The 67 remaining patients had received some type of antisyphilitic treatment prior to their present admission and had subsequently evidenced relapse or inadequate resolution of their initial lesions. The previous treatment consisted of inadequate or adequate

4. Bauer, T. J.; Bundesen, H. N.; Craig, R. M.; Schwemlein, G. X., and Barton, R. L.: The Treatment of Early Syphilis with 600,000 Units of Penicillin in Seven and One-Half Days, Am. J. Syph., Gonor. & Ven. Dis. **31**:45 (Jan.) 1947.

5. Craig, R. M.; Schwemlein, G. X.; Barton, R. L.; Bauer, T. J., and Bundesen, H. N.: Penicillin in the Treatment of Early Syphilis: Four Hundred and Twenty-Nine Patients Treated with 1,200,000 Units in Ninety Hours, to be published.

metal chemotherapy, administration of penicillin alone and penicillin in combination with metal chemotherapy and/or artifically induced fever.

TABLE 1.—*Number and Percentage of Patients, Grouped by Race, Sex and Age*

Race and Sex	Number				Percentage			
	Total	Under 20	20-24	Over 24	Total	Under 20	20-24	Over 24
Total	324	63	115	146	100.0	100.0	100.0	100.0
Male	176	24	40	112	54.3	38.1	34.8	76.7
Female	148	39	75	34	45.7	61.9	65.2	23.3
White	66	7	14	45	20.4	11.1	12.2	30.8
Male	39	2	4	33	12.1	3.2	3.5	22.6
Female	27	5	10	12	8.3	7.9	8.7	8.2
Negro	258	56	101	101	79.6	88.9	87.8	69.2
Male	137	22	36	79*	42.3	34.9	31.3	54.1
Female	121	34	65	22	37.3	54.0	56.5	15.1

* Including 1 Japanese.

TABLE 2.—*Number and Percentage of Patients, Grouped by Diagnosis*

Diagnosis	Number	Percentage
Total	324	100.0
Primary seronegative	36	11.1
Primary seropositive	69*	21.3
Secondary	176†	54.3
Relapsing	43	13.3

* Including 14 patients with reinfection.
† Including 5 patients with reinfection.

TABLE 3.—*Number of Patients Observed, with Treatment Results Grouped by Number of Days from Beginning of Treatment*

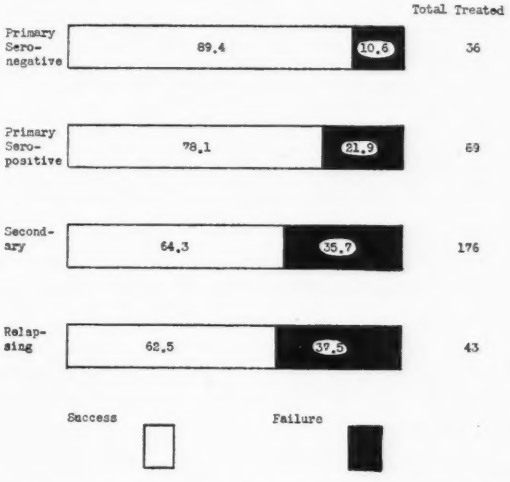
Number of Days from Beginning of Treatment	Number of Patients			
	Total Observed During Period or Later	Serologic Titer		Failures Found During Period
		Negative	Positive	
1- 29	316	35	281	..
30- 59	285	65	220	..
60- 89	270	98	169	3
90-119	256	109	139	8
120-149	243	119	113	11
150-179	223	127	91	5
180-209	208	137	63	8
210-239	189	133	53	3
240-269	185	139	41	5
270-299	173	135	37	1
300-329	164	130	31	3
330-359	149	122	26	1
360-449	136	117	12	7
450-539	94	88	1	5

The results of treatment are summarized in table 3 and demonstrated graphically as applied to the whole group and the stage of the disease at the time the treatment was instituted. The cumulative failure rate was 10.6 per cent among 36 patients with primary seronegative syphilis,

21.9 per cent among 69 patients with primary seropositive syphilis, 35.7 per cent among 176 patients with untreated secondary syphilis and 37.5 per cent among 43 patients who had had previous treatment and subsequently showed infectious relapse. The over-all cumulative failure rate, regardless of diagnosis, was 29.6 per cent at the end of one year's observation.

The percentages used for the success and failure graph were obtained by assuming that patients lost from observation would have shown the same ratio of treatment results as those observed.

Patients with positive significant serologic titers (4 Kahn units or more) after twelve months have been grouped with those in whom



Percentage of success and failure at the end of the first year's observation.

treatment was a failure. For those who were seronegative or maintained nonsignificant titers treatment, for the time being, was considered successful.

One hundred and seventy-one (59.4 per cent) of the seropositive patients achieved seronegativity during the year after treatment. Sixteen (9.4 per cent) of these subsequently relapsed. Seven patients were retreated because of pregnancy.

A lumbar puncture was performed on all but 10 of the 324 patients prior to treatment. There were 66 patients with group I and 7 with group II spinal fluid, the determinations being made according to the criteria of Moore.[6] In this group of 73, examinations were repeated

6. Moore, J. E.: The Modern Treatment of Syphilis, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1941, p. 416.

for 27 patients at six month to one year intervals. Seven had normal fluid, 16 group I and 4 group III.

For 60 of the total number of patients treated the result was known to be a failure. These consisted of 3 with relapsing primary syphilis, 7 with primary syphilis progressing to secondary syphilis, 21 with relapsing secondary syphilis and 29 with serologic relapse.

Among the 60 in whom treatment was a failure, 16 had an abnormal spinal fluid before treatment. There were 15 patients with group I and 1 patient with group II cerebrospinal fluid. One had no pretreatment lumbar puncture. Of the 43 patients with normal pretreatment spinal fluid, 38 were reexamined at the time of failure; 1 had group I fluid, 2 group II and 1 group III.

In our present state of knowledge it is futile to attempt to separate reinfection from relapse, and therefore all recurrences of syphilis are grouped as treatment failures. It is recognized, however, that some of the patients may well have been reinfected.

There were no serious complications resulting from the treatment administered, and in no patient was treatment discontinued because of an untoward manifestation exhibited during the course of the treatment.

The results presented in this paper must be interpreted in the light of the fact that from June 1943, the date of inception of the study, to the present time commercial penicillin has been a changing mixture of various substances. The content of "impurities" has gradually decreased as potency, in terms of units per milligram, has increased. The relative amounts of the several identified penicillin fractions, G, F, and K, have likewise varied from time to time. Those two changes, and perhaps others, suggest that therapeutic efficacy may not have remained constant and that it may be significantly different today from what it was orginally. It is not now possible to assess the extent to which these changes may have affected the results here reported.

SUMMARY

Three hundred and twenty-four patients with dark field positive syphilis were treated over a seven and one-half day period, each receiving 1,200,000 units of penicillin.

For 60 of these treatment was known to be a failure during a minimum observation period of eighteen months for each patient.

The cumulative failure rate, disregarding stages of the disease, was 29.6 per cent.

CONCURRENT MELANOSIS AND HYPERTRICHOSIS IN DISTRIBUTION OF NEVUS UNIUS LATERIS

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SOME PLAQUES of localized melanosis appear early in life and are probably of prenatal origin. Acquired localized melanosis appears on various parts of the body. Melanosis calorica follows local exposure to heat. Irradiation by ultraviolet rays, alpha rays from thorium X, roentgen or radium rays is followed by melanosis in the exposed area. Certain volatile oils, such as oil of lime, when applied locally sensitize the skin to ultraviolet irradiation, as was reported by Sams.[1] Industrial melanosis results in part from photosensitization by various substances derived from crude coal tar and is observed predominantly on exposed surfaces. Postinflammatory melanosis is limited to the areas involved in inflammation. A thermal or chemical burn of the palm is at times followed by a patchy melanotic plaque.

Localized melanosis of internal origin is observed in the form of chloasma, often limited to the face and neck. This localized disorder has also been reported in association with hyperthyroidism, tuberculosis, sprue, Gaucher's disease and other systemic diseases. Chloasma of pregnancy has a more generalized distribution.

According to Galewsky,[2] localized hypertrichosis has followed temporary and prolonged cutaneous irritation by strong mercurial ointment U. S. P. or tincture of iodine with subsequent wet dressings and has occurred after burns, in the area of the scar, and after morphea. Light and sun are factors in its production in sailors.

Various nevi are involved in hypertrichosis. Scholtz [3] stated that there is no sharp division between simple nevi pigmentosi et pilosi

From the Section of Dermatology, The School of Medicine, University of Chicago.

1. Sams, W.: Photodynamic Action of Lime Oil (Citrus Aurantifolia), Arch. Dermat. & Syph. **44**:571 (Oct.) 1941.

2. Galewsky, E.: Erkrankungen der Haare und des Haarbodens, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1932, vol. 13, pt. 1.

3. Scholtz, W.: Naevi, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1932, vol. 12, pt. 2.

and verrucous nevi with a heavy growth of hair. He suggested the designation "hypertrichosis" for hairy nevi without pigment and seemed to imply that pigmented hairy plaques are nevi. I have observed 2 patients with a similar history and the identical unusual clinical disorder, which has been studied microscopically.

REPORT OF CASES

CASE 1.—G. B., a boy aged 17, had had alopecia areata at the age of 12, with recurrence of the disorder at 16. At the age of 11, after severe sunburn, a blotchy

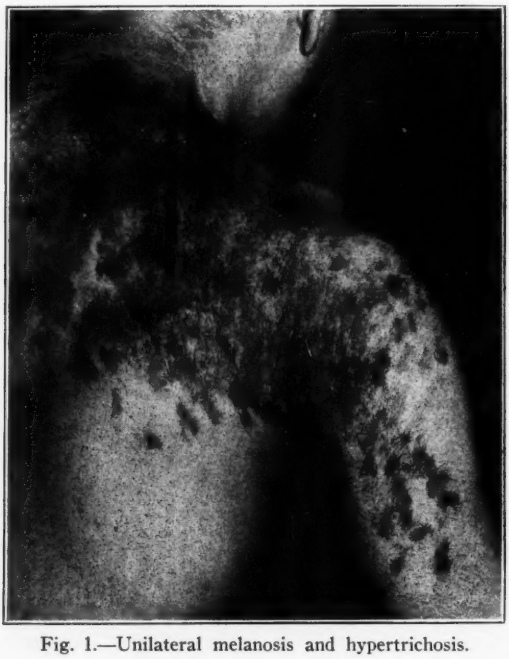

Fig. 1.—Unilateral melanosis and hypertrichosis.

brown area developed over the right shoulder. Two years later, hair grew in the area. Since that time, the patient had been treated for nephrolithiasis, injury to the semilunar cartilage of the right knee and Bell's palsy.

Clinical Examination.—There was patchy, light brown pigmentation over the right shoulder, extending from the midline down onto the arm (fig. 1). The central area was more diffuse, while the periphery showed islands of hyperpigmentation with their long axes in the lines of cleavage. The pigmentation appeared more pronounced about the follicles. In the pigmented plaques were numerous short, heavy, black hairs, their presence more pronounced near the center. There were no subjective symptoms. For this reason, and because the area was covered by the clothing, no treatment was attempted.

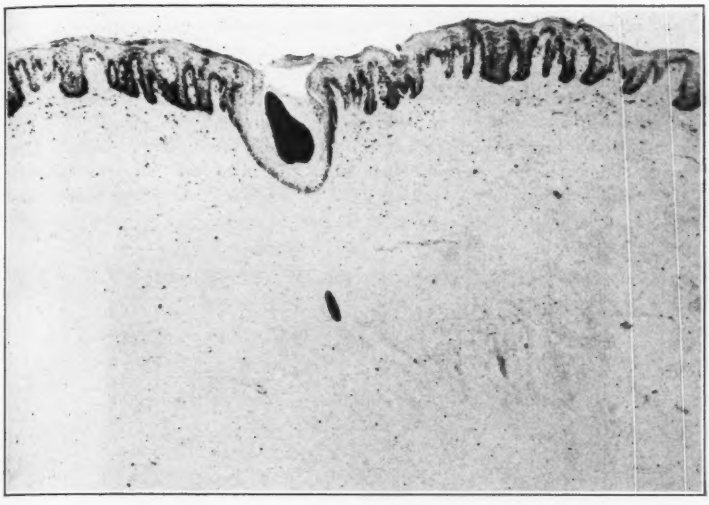

Fig. 2.—A large, deeply pigmented hair with surrounding melanosis (silver nitrate reaction; low power lens).

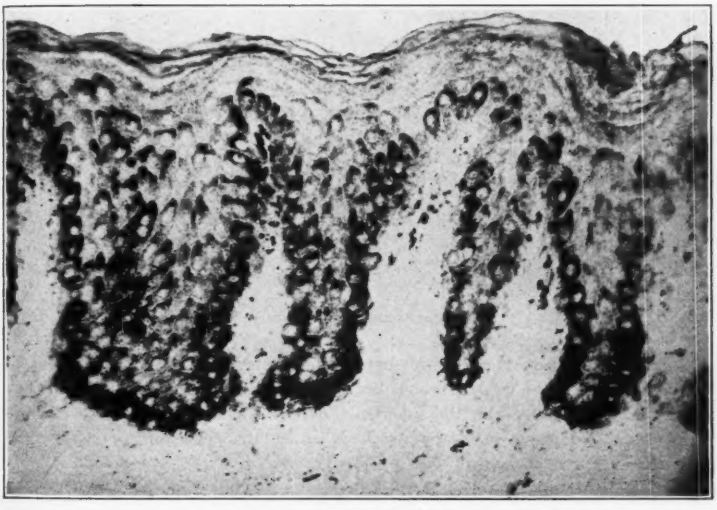

Fig. 3.—Epidermal melanosis with little sign of pigment activity. Papillary and dermal chromatophores are evident. No nevus cells are seen (silver nitrate reaction; low power lens).

Microscopic Examination.—Sections stained with hemalum, erythrosin and saffron revealed no alteration of the epidermis or dermis, except that there was increased pigment in the basal portion of the epidermis. Sections treated with a 2 per cent solution of silver nitrate for two hours and fixed with a cold saturated solution of sodium thiosulfate for two minutes showed a large, heavily pigmented hair, with increased melanin in both the epidermis and the superficial dermis (fig. 2). Under high power (fig. 3), the basal cells were seen to contain large amounts of melanin, the pigment often filling the entire cell with the exception of the nuclear region. In some of the basal cells and in some of the more superficial cells, the melanin was localized in nuclear caps. Melanin granules were seen

Fig. 4.—Unilateral melanosis and hypertrichosis.

in decreasing numbers in the more superficial cells, even in the stratum corneum. It was difficult to identify melanoblasts, and no dendritic melanoblasts were apparent. The papillae and the superficial dermis contained melanin-laden chromatophores. No nevus cells were seen in either the epidermis or the dermis. The diagnosis was melanosis with hypertrichosis.

Case 2.—E. U., a man aged 24, stated that six years previously he had experienced severe sunburn on the back. The inflammation had been followed by the appearance of blotchy brown pigmentation and, later, by growth of hair in the area. The patient believed that the brown of the pigmented plaque was gradually becoming lighter. There were no subjective symptoms.

Clinical Examination.—Blotchy pigmentation and hypertrichosis were seen on the upper right portion of the back, extending from the midline to the posterior axillary line. There was a more diffusely pigmented plaque on the upper portion of the back, near the midline, with isolated plaques arranged along the lines of cleavage downward and outward (fig. 4). Follicular hyperkeratosis, which appeared more pronounced in the pigmented areas, was present. The pigment itself appeared to be more abundant in the perifollicular regions (fig. 5).

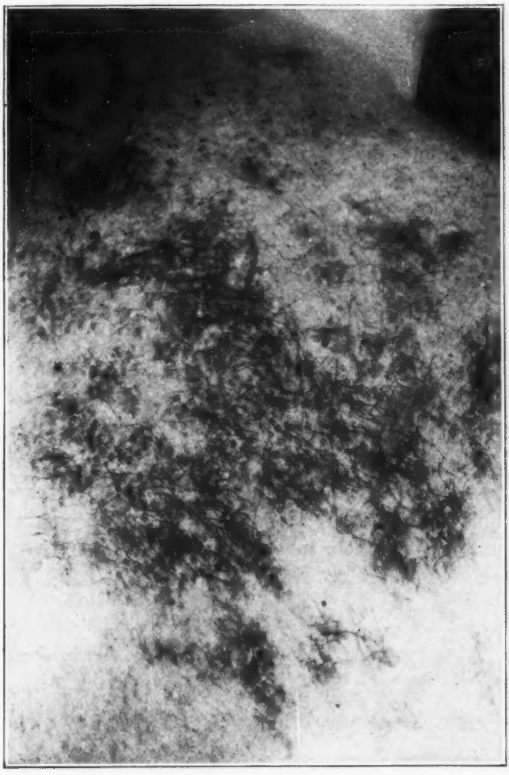

Fig. 5.—Unilateral melanosis and hypertrichosis.

Microscopic Examination.—The observations were essentially the same as in case 1.

COMMENT

Since the terms "nevus" and "nevoid" have been used rather loosely, the disorder observed in the 2 patients could be called "acquired nevus pigmentosus et pilosus." In an effort to establish pathologic designations for various forms of nevi, such as those of the vascular variety,

Becker and Obermayer [4] stated, "Thus we suggest that the term nevus should be used only to designate nevus unius lateris and nevus pigmentosus." Nevus pigmentosus always contains nevus cells. They suggested confining the designation of nevus unius lateris to three types of disorder: (1) verrucous, (2) keratotic and (3) comedonicus. On this basis, the condition reported in this paper would not qualify for the diagnosis of nevus. For this reason, the designation "melanosis and hypertrichosis in distribution of nevus unius lateris" was employed. The preexisting sunburn in both instances is interesting and may have played a role in causing the disorder. However, sunburn in itself is not a sufficient cause, as is evidenced by numerous cases in which melanosis and/or hypertrichosis does not supervene. One might assume activation of an abnormal subclinical process by the intense sunburn. Hypertrichosis in sailors is more diffuse and is bilateral.

SUMMARY

Two cases of an unusual combination of acquired melanosis and hypertrichosis in unilateral distribution are presented. In both instances, the disorder was preceded by severe sunburn. Microscopic examination revealed no nevus cells, either epidermal or dermal.

ADDENDUM

NOTE.—Since completion of this report, additional information has been received from the patient in case 2. There is no similar condition in the parents, grandparents, four uncles, an aunt, a sister or three nephews. The patient stated that the pigmentation continued to fade until, now that he is 35 years old, the disorder represents unilateral hypertrichosis without melanosis.

55 East Washington Street (2).

4. Becker, S. W., and Obermayer, M. E.: Modern Dermatology and Syphilology, ed. 2, Philadelphia, J. B. Lippincott Company, 1947.

PYODERMA VEGETANS IN ASSOCIATION WITH CHRONIC ULCERATIVE COLITIS

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AND
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ONE OF the most dreaded complications of chronic ulcerative colitis is the fulminating ulcerative process of the skin known as pyoderma gangrenosum.[1] Although such symptoms occasionally may precede diarrhea by weeks or months, they usually become manifest only after disability of the systemic process has been well established. In such cases, the skin is hypersensitive to trauma and infection, the lesions proceed in parallel with the degree of activity of the colitis and the prime factor in successful treatment consists of control of the underlying disease. Occasionally other complications of the skin may appear, namely, furuncles or episodes of erythema nodosum and erythema multiforme.[2]

The purpose of this report is to record 5 cases in which chronic ulcerative colitis was associated with a recalcitrant pyogenic process of distinctive pattern, resembling pemphigus vegetans or dermatitis vegetans of the type described by Hallopeau [3] as *pyodermite végétante.*

REPORT OF CASES

CASE 1.—A boy aged 15 had come to the clinic in September 1939 because of bloody diarrhea. He had had three to twenty bowel movements daily for the

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Dr. Brunsting is from the Section on Dermatology and Syphilology, Mayo Clinic.

1. Brunsting, L. A.; Goeckerman, W. H., and O'Leary, P. A.: Pyoderma (Echthyma) Gangrenosum: Clinical and Experimental Observations in Five Cases Occurring in Adults, Arch. Dermat. & Syph. **22**:655-680 (Oct.) 1930. O'Leary, P. A.; Montgomery, H., and Brunsting, L. A.: A Group of Cases of Pyoderma with Various Systemic Manifestations, ibid. **41**:752-753 (April) 1940.

2. (*a*) Bargen, J. A.: Complications and Sequelae of Chronic Ulcerative Colitis, Ann. Int. Med. **3**:335-352 (Oct.) 1929. (*b*) Ricketts, W. E., and Palmer, W. L.: Complications of Chronic Non-Specific Ulcerative Colitis, Gastroenterology **7**:55-66 (July) 1946.

3. Hallopeau, M.: Nouvelle étude sur une forme pustuleuse et bulleuse de la maladie de Neumann, dite pemphigus végétant, Ann. de dermat. et syph. **29**:969-976, 1898.

three years previously. Proctoscopic examination revealed that the bowel was scarred and contracted and the mucosa was granular and bleeding. Roentgenograms disclosed definite shortening and deformity of the entire colon. The pathologic process was interpreted as active chronic ulcerative colitis. Results of the remainder of the clinical examination were negative.

Laboratory procedures did not reveal significant abnormalities. Results of urinalysis were negative. The value for hemoglobin was 13.1 Gm. per hundred cubic centimeters; there were 4,660,000 erythrocytes and 7,600 leukocytes per cubic millimeter of blood. Result of the serum flocculation test for syphilis was negative. The blood sedimentation rate (Westergren) was 25 mm. in one hour. Examination of the stools revealed no ova or parasites; culture did not produce Bargen's streptococcus. Roentgenograms of the sinuses, teeth and thorax showed nothing abnormal. When the patient was dismissed, a program of supportive treatment was outlined for him.

He returned to the clinic in October 1945 because of persistent bloody diarrhea and mucocutaneous lesions. He had had about seven daily bloody bowel move-

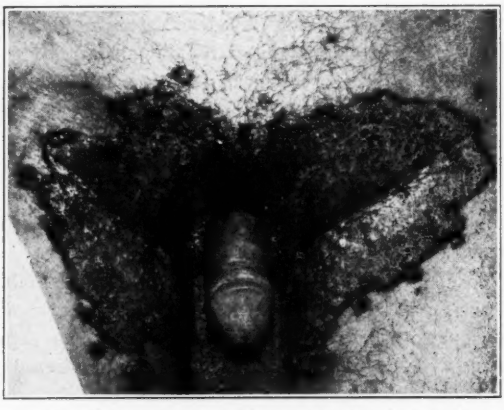

Fig. 1 (case 1).—Vegetating dermatitis in the inguinal regions, with minute vesicopustules studding the margins of the plaque. Specimen for biopsy was taken from the site on the right. Picture was made during the patient's 1945 visit to the clinic.

ments, associated with loss of 15 pounds (6.8 Kg.) and increasing fatigue. In the preceding eighteen months superficial ulcerations had appeared on the buccal mucosa, lips and gums, with pustular lesions developing on the trunk. During the six months prior to his visit the last-mentioned lesions healed, except for pustular, vegetative plaques in the groins (fig. 1) and right axilla. Pruritus was not a predominant symptom. Treatment had consisted of sulfadiazine and succinylsulfathiazole (sulfasuxidine®) administered orally, roentgen therapy and administration of staphylococcus toxoid. The toxoid had brought about urticaria and fever. All the foregoing measures were without benefit.

Cutaneous examination of the patient at the clinic revealed several white plaques and superficial inflammatory ulcerations on the mucosa of lips, gums and oral cavity. There was moderate crusting of the nasal vestibules. In the genitocrural folds and right axilla were vegetative and pustular plaques, in the margins of which were small vesicopustules. Active chronic ulcerative colitis

was discovered by proctoscopic studies and roentgenograms; results of the remainder of the general examination were negative.

Laboratory examinations carried out at the second admission of the patient gave these results. Those of urinalysis were negative. The value for hemoglobin was 12.1 Gm. per hundred cubic centimeters of blood. There were 4,820,000 erythrocytes and 7,300 leukocytes per cubic millimeter of blood, with a moderate shift to the left in polymorphonuclear leukocytes. The result of the flocculation test for syphilis was negative. The value for total proteins was 7.2 Gm. per hundred cubic centimeters of serum, and the content of vitamin C was 1.3 mg. per hundred cubic centimeters of blood. The sedimentation rate (Westergren) was 33 mm. in one hour. A roentgenogram of the thorax revealed nothing abnormal. Smears, and culture of material, from the mucocutaneous lesions revealed Staphylococcus

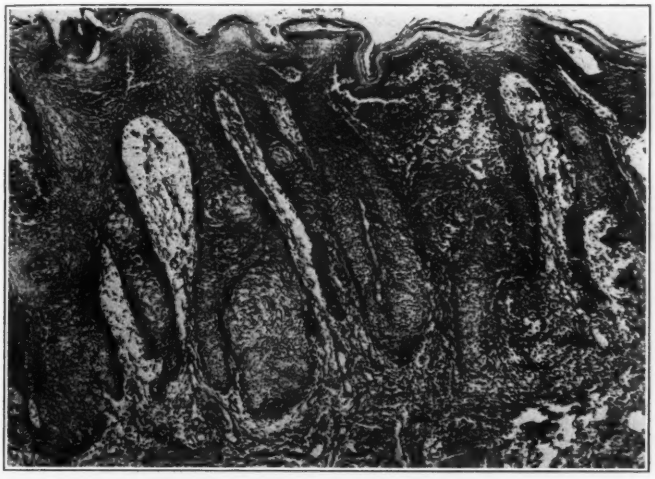

Fig. 2 (case 1).—Pseudoepitheliomatous hyperplasia with a pronounced cellular infiltrate, predominantly eosinophilic leukocytes (hematoxylin and eosin, × 50).

aureus, a hemolytic type of streptococcus, green-producing streptococci and a species of Corynebacterium. Study of smears and culture of material for fungi gave negative results.

Biopsy of material from the lesion in the groin revealed a hyperkeratotic and parakeratotic stratum corneum. There was pronounced acanthosis, with spongiosis and intracellular edema. Long narrow rete pegs projected into the cutis, and leukocytes invaded the prickle cell layers, which presented frequent mitotic figures. The basal cell layer exhibited liquefaction degenerative changes resulting from advanced cellular infiltration into the upper cutis and papillary bodies. The cutis was edematous and contained dilated vessels. The cellular infiltrate was constituted predominantly of eosinophilic leukocytes (fig. 2). In the midcutis the collagenous fibers were somewhat homogenized and thickened. There was an increase in fibroblasts. Elastic fibers were present in the cutis. The sweat glands were edematous; the sebaceous glands were surrounded by connective-tissue cellular infiltrate.

In summary, the chief pathologic observations consisted in pseudoepitheliomatous hyperplasia with a definite eosinophilic infiltrate in the upper cutis. These observations were consistent with pemphigus vegetans, dermatitis vegetans, *pyodermite végétante* of Hallopeau or nonspecific granuloma.

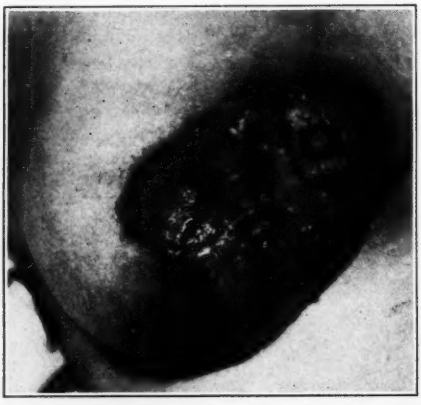

Fig. 3 (case 2).—Chronic vegetating pyoderma of the right breast of three months' duration.

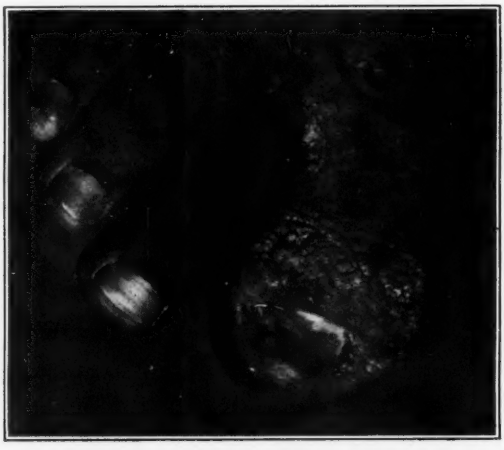

Fig. 4 (case 2).—Lesion of the right great toe of six weeks' duration, showing papillomatous overgrowth extending from paronychia.

In the hospital the course of the patient was afebrile. There was gradual improvement over a period of six weeks, but this was followed by exacerbation of the lesions in the groin before the patient was dismissed. The symptoms of colitis abated moderately. Treatment in the hospital consisted of a special diet for chronic ulcerative colitis and the administration of oxophenarsine hydrochloride,

azosulfamide (neoprontosil®), phthalylsulfathiazole (sulfathaladine®), general ultraviolet irradiation, the parenteral administration of amino acids and the use of multivitamin supplements. Blood was transfused several times. Local treatment included the use of potassium permanganate wet dressings and baths, acriflavine mouth wash, methylrosaniline chloride, wet penicillin dressings and a soothing shake lotion. The dermatologic diagnosis favored an unusual type of vegetating pyoderma suggesting dermatitis vegetans or pemphigus vegetans. The condition did not present the usual characteristics of pyoderma gangrenosum.

Six months later the patient reported that an exacerbation of the lesions involving the scalp, eyelids, groins and axillas had occurred. On three occasions the

Fig. 5 (case 4).—Involvement of right axilla, showing discrete vaccinia-like lesions and vegetative pustular plaques; six months' duration.

lesions exhibited renewed activity after use of phthalylsulfathiazole. In retrospect, it was recalled that the drug had been used during the patient's last nine days in the hospital, at which time there had been a recurrence of the lesions in the groin. After this exacerbation while the patient was home, the lesions gradually abated, and in May 1946 active lesions were reported to be present only in the nose and mouth. General supportive treatment had been employed. In March 1947 the patient reported that his skin was clear and that his general health was much improved.

Case 2.—A married woman aged 31 came to the clinic in May 1942, three months post partum, because of lesions of the mouth, external nares and right

great toe and an infection on the breast. The oral lesions had been present nine years, and the most recent lesion on the toe, for six weeks. There had been an average of five watery bowel movements a day during the seven months prior to the patient's visit to the clinic. The most severe attack occurred three weeks post partum, followed within ten days by exacerbation of the lesions.

Examination of the gums revealed multiple white plaques with inflammatory areolas and bloody crusts about the external nares. The lesion on the breast was a palm-sized, gyrate and vegetative erythematous plaque with small abscesses in the margins (fig. 3). The right great toe was an inflamed, pustular mass without a nail (fig. 4). There was a shallow, irregular erosion near the clitoris.

Results of the general examination were noncontributory, except for mild chronic ulcerative colitis as demonstrated by proctoscopic and roentgenologic studies. The laboratory examinations disclosed nothing abnormal except for eosinophilia in which eosinophils amounted to 14 per cent. The sedimentation rate (Westergren) reached a maximum of 90 mm. in one hour. Green-producing streptococci, Staphylococcus albus and micrococci were found on culture of material from the lesions. Results of examinations for fungi were negative.

While the patient was in the hospital regression of the cutaneous lesions occurred coincident with abatement of the diarrhea. She returned to the clinic in March 1943 because of exacerbation of the lesions on the great toe and in the mouth, after a recurrence of bloody diarrhea. The lesions at this time were much the same as previously noted. The proctoscopic observations were similar to those recorded in May 1942. During hospitalization of the patient the lesions on the skin, except on the toe, gradually subsided. The lesion on the toe gradually responded to therapy, including roentgen treatments. The patient reported by letter six months later that the lesion on the toe would not heal.

CASE 3.—A married woman aged 25 came to the clinic in October 1944 because of recurring, painful, red, "infected" gums and sublingual "blisters" of four years' duration. Three months before she was admitted, after episiotomy at delivery of a child, a fungating lesion had developed in the wound and the axillas had become "infected." There had been recurring attacks of diarrhea for three years. During pregnancy there usually had been four watery, mucosanguineous stools daily; more severe exacerbations occurred post partum.

At the clinic, inflammatory vesicopustules were noted on the gums and floor of the mouth of the patient. Fungating, verrucous and pustular plaques were present in the axillas. A fungating pyodermic plaque was situated on the right side of the perineum. Results of examinations for fungi were negative. Active chronic ulcerative colitis was found by proctoscopic and roentgenologic studies; results of the remainder of the general examination were negative. Laboratory procedures revealed nothing abnormal except for a sedimentation rate (Westergren) of 40 mm. in one hour. The patient's course was afebrile except for a brief rise in temperature to 103 F., which was related to carbarsone therapy; only slight abatement of the diarrhea and the lesions of the skin was noted while the patient was hospitalized.

CASE 4.—A man aged 31 came to the clinic in June 1946 because of lesions of the skin of the hands, left nostril and right axilla of six months' duration. Since the age of 16 years this patient had had two to five loose bowel movements daily, with more severe exacerbations in the two years prior to his admission. Before coming to the clinic, the patient had received injections of penicillin, roentgen therapy and sulfathiazole administered orally, without benefit.

At the clinic several asymmetric vegetative pustular lesions were noted on the hands and fingers of the patient. Many draining purulent lesions and three vegetative and pustular plaques were noted in the right axilla (fig. 5). Inflammatory erosion was present at the left nostril. The patient's temperature was normal.

Active chronic ulcerative colitis was discovered by proctoscopic and roentgenologic studies. Results of other examinations were noncontributory. Culture of material from the lesions produced hemolytic streptococci and micrococci. Results of examination for fungi were negative. Results of inoculation of animals to demonstrate virus were negative. The value for hemoglobin was 10.5 Gm. per hundred cubic centimeters of blood, and the sedimentation rate (Westergren) was 25 mm. in one hour. Other laboratory procedures gave normal results.

The patient returned home before treatment was instituted. His home physician reported that improvement did not result from the administration of acetarsone, phthalylsulfathialzole, sulfathiazole and oxophenarsine hydrochloride or the use of a high vitamin diet and antiseptic agents applied locally.

Case 5.—A man aged 43 years came to the clinic in October 1946 because of cutaneous lesions of eighteen months' duration. He had had intermittent bloody diarrhea for fifteen years and a chronic nasal discharge with an indolent ulcer of the nasal vestibule for six years. In July 1945, after conjunctivitis and exacerbation of the nasal discharge, an exudative pustular eruption had occurred in the bearded area, upper lip, mouth, neck and umbilicus. Treatment elsewhere had consisted of the injection of penicillin, oral administration of sulfonamide and arsenic compounds, and the use of ultraviolet and roentgen irradiation. Except for the lesions of the nose and lip, considerable improvement had occurred by March 1946. In June 1946, a recurrence involved the bearded area, and the tissues of the left great toe had become a vegetative, exudative, purulent mass.

Cutaneous examination of the patient at the clinic revealed an exudative, crusted, erythematous and pustular eruption of the bearded area. The nose, which was bulbous, was studded with vesicopustules. Serpiginous nonulcerative whitish plaques were noted on the hard palate.

Proctoscopic and roentgenologic procedures disclosed chronic ulcerative colitis; results of the remainder of the general examination were normal. Laboratory procedures gave negative results except that the value for hemoglobin was 9.8 Gm. per hundred cubic centimeters of blood, eosinophilic leukocytes amounted to 26 per cent and the maximal sedimentation rate (Westergren) was 55 mm. in one hour. Streptococci, hemolytic and nonhemolytic types, and Staph. aureus were found on culture of material from the lesions of the skin. The hemolytic types of streptococci were sensitive to less than 0.05 units of penicillin per cubic centimeter. The growth of Staph. aureus was not inhibited by 1.6 units of penicillin per cubic centimeter. Results of examination for fungi were negative.

Biopsy of a specimen of tissue from a lesion on the patient's neck revealed the epidermis to be both atrophic, due to pressure from an underlying abscess, and acanthotic with spongiosis. The upper cutis was edematous, and there was a decided infiltrate composed predominantly of polymorphonuclear leukocytes and eosinophils. The epidermis was invaded by the infiltrate, which also surrounded the dermal appendages. In summary, the pathologic observations were consistent with the presence of an acute abscess.

Minimal improvement of the skin was noted, although the bowel function was normal during hospitalization of this patient.

Comment.—Data on 5 patients who had the clinical syndrome of chronic ulcerative colitis and vegetating pyoderma have been presented. The ages of the patients ranged from 21 to 43 years. Two patients were women; the onset of their cutaneous lesions had followed childbirth. Of all lesions, those of the mucous membranes (especially in the mouth) were present the longest, for nine years in case 2. The oral lesions preceded symptoms of colitis by one year (case 3) and by eight and a half years (case 2) as far as the women are concerned. However, the men in this study had had symptoms of colitis preceding the lesions of the skin or mucous membranes by more than seven to fourteen years. The shortest duration of cutaneous lesions was six months, and the longest, fifteen months. Duration of the symptoms of colitis ranged from seven months to fifteen years. In at least 4 of the 5 patients there seemed to be a definite relation between relapse of the cutanous lesions and exacerbation of the symptoms of colitis.

The sites of the lesions were the mouth, external nares, axillas, genitocrural area, fingers or toes, face and neck, umbilicus, breast and scalp. All these areas were not involved in each patient, as noted. The oral lesions in these cases consisted of white plaques, inflammatory erosions and, in 1 patient, vesicopustules. The lesions of the skin were vegetative, exudative, crusting and erythematous plaques with vesicopustules in the margins.

Hemolytic and nonhemolytic types of streptococci, Staph. aureus, Staph. albus and micrococci were found by culture of material from the lesions. Results of inoculation of animals were negative for vaccinia and herpes virus in case 4. Results of examination for fungi were negative in these cases. Examinations of stools did not disclose pathogens.

Routine laboratory tests, including blood counts, urinalyses, serologic tests for syphilis and roentgenograms of the thorax gave negative results, except as noted. Hemoglobin values of 10.5 and 9.8 Gm. per hundred cubic centimeters were obtained in cases 4 and 5, respectively. Eosinophils amounted to 14 and 26 per cent of leukocytes in cases 2 and 5, respectively. The sedimentation rate was elevated in all cases, the maximal reading being 90 mm. in one hour (Westergren) in case 2. Proctoscopic examinations and roentgenograms of the colon disclosed chronic ulcerative colitis in all cases, the severest involvement occurring in case 1, with appreciable shortening and deformity of the colon.

Histopathologic examinations were made in cases 1 and 5, but the results were not diagnostic for a specific clinical entity. In case 1 the lesion in the groin was interpreted as a nonspecific granuloma or pemphigus vegetans or dermatitis vegetans, revealing many eosinophils

and pseudoepitheliomatous hyperplasia. In case 5 biopsy of a specimen from a lesion on the neck disclosed an acute abscess, consisting of eosinophilic and polymorphonuclear leukocytic infiltrate of the epidermis and cutis.

In all cases the patients responded slowly, if at all, to treatment. All were afebrile during observation except in case 3, in which instance the fever seemed to be related to a brief trial of carbarsone therapy. The longest hospitalization period was sixty-four days and the shortest, twenty-four days. The most commonly used measures were courses of acetarsone, azosulfamide, phthalylsulfathiazole and oxophenarsine hydrochloride, the transfusion of blood and ultraviolet irradiations. Roentgen treatment was administered to the lesion on the toe in case 2, with but temporary benefit. Topical treatment consisted of the use of various antiseptic solutions and ointments. A total of 4,800,000 units of penicillin was employed in case 5, without definite response. Bland, high vitamin, high protein diets were employed for the chronic ulcerative colitis. Often there were remissions in the lesions followed by exacerbations, frequently associated with renewed activity of the colitis. Improvement of the general health of the patient and control of the underlying colitis appeared to be of great importance.

CUTANEOUS DIFFERENTIAL DIAGNOSIS

Pemphigus vegetans may simulate the conditions reported in the foregoing cases. The sites of predilection of pemphigus and the aforementioned conditions may be similar, with involvement of the mucous membranes of the mouth, nose, genital area, axillas, digits, breasts, umbilicus and scalp. The lesions, although as a rule initially bullous, as in other forms of pemphigus, quickly become erosions, ulcerations or vegetative lesions. Remissions and exacerbations are common. The general health of some patients may be more profoundly affected than it was in our patients. The true type of pemphigus vegetans as described by Neumann [4] is invariably fatal. The typical histopathologic picture consists of acanthosis, papillomatosis with microabscesses, located in epidermis and papillary bodies and composed mainly of an eosinophilic leukocytic infiltrate. The conditions in the cases we have reported suggested pemphigus vegetans, but the absence of supportive observations of bullae, the lack of the usual pemphigus type of constitutional symptoms and the continued observation of, and definite association of the various conditions with, chronic ulcerative colitis made this diagnosis untenable.

4. Neumann, J., cited by Darier, J.: A Textbook on Dermatology, translated from the second French edition, Philadelphia, Lea & Febiger, 1920, p. 244.

Hallopeau [3] described the condition which he named *pyodermite végétante* in 1898. The cutaneous manifestations which he described resemble those observed in our patients. Hallopeau presented the disease as one of unknown etiology, the eruption occurring in adult persons on the genital organs, lips, mouths, fingers and, less frequently, on the scalp, neck, back and extremities. The primary lesion is a vesicopustule on an inflammatory base, which spreads by peripheral growth. Crusts form centrally and on separation leave a reddened exuberant surface. The tendency to form vegetative lesions is predominant, and suppuration frequently is appreciable. The eruption is asymmetric; on involution there remain reddish macules or pigmentation at the sites of former patches. Generally, the condition is benign, the patient afebrile and his general health good. Pronounced itching and response to antiseptic treatment, except for the more obstinate lesions of the mouth and nose, are mentioned. Microscopic examination reveals epidermic proliferation with the formation of vesicles, edematous papillae and a predominantly eosinophilic infiltrate. Hallopeau later believed *pyodermite végétante* and pemphigus vegetans were similar, and he described them under the term Neumann's disease.[5]

The possibility of coccogenous sycosis was briefly considered in case 5 because of the dermatitis on the face. However, the combination of the lesions of the umbilicus, toe and mucous membranes with the symptoms of colitis suggests this etiologic association. Other types of vegetating dermatoses may be mentioned but were eliminated in our cases. There was no history of the ingestion of iodides or bromides to account for the vegetative lesions. The clinical picture did not support a diagnosis of vegetative dermatitis herpetiformis. Results of examinations for fungi, such as those which cause blastomycosis, were negative in these cases.

Dermatitis vegetans should be considered not a disease entity but a dermatosis with multiple causes. Usually there is prompt response to antiseptic or other properly directed therapy. Tuberculosis verrucosa cutis, impetigo herpetiformis and condyloma latum may cause vegetative lesions but were eliminated in these cases.

COMMENT

O'Leary, Montgomery, Goeckerman and one of us (Brunsting),[1] as well as Bargen,[2a] have briefly mentioned vegetative dermatitis complicating chronic ulcerative colitis. Pernet [6] discussed a case in which

5. Hallopeau and Leredde, cited by Jamieson, W. A.: Dermatitis Vegetans, Brit. J. Dermat. **4**:407-417 (Nov.) 1902.

6. Pernet, G.: Dermatitis Pustulosa Vegetans Recurrens, J. Cutan. Dis. **30**:517-523 (Sept.) 1912.

vegetative dermatitis was associated with "colitis." Warner [7] presented a case in which a child aged 7 had chronic ulcerative colitis complicated by a bullous or sometimes a crusted eruption of the skin and mucous membranes which resembled "benign pemphigus." Cole and Driver [8] described an instance of dermatitis vegetans associated with occult blood in the stools involving a history of persistent diarrhea of unknown cause two years previously. Special studies of the colon were not made. Goldsmith [9] for eight years observed a patient who experienced recurrent episodes of dermatitis classified as *pyodermite végétante* (Hallopeau), associated with recurrent episodes of mucosanguineous diarrhea diagnosed as "spastic colitis." Proctoscopic examinations or roentgenograms of the colon were not made. Heisel and Krause [10] presented a case of pemphigus vegetans without mention of colitis or other constitutional symptoms. At necropsy, superficial ulcerations in the large intestine and esophagus as well as cloudy swelling of the liver and kidneys and bronchopneumonia were found.

The cutaneous manifestations which occur in chronic ulcerative colitis may be variable in character and severity. Dermatitis (pyoderma) vegetans is a dermatosis of multiple causes, and in chronic ulcerative colitis it represents a cutaneous pattern which is but one expression of several forms which may be observed. These include furunculoid lesions, erythema nodosum, exanthematous eruptions, erythema multiforme and the classic liquefying and necrotic ulcerations known as pyoderma gangrenosum.

The bacteriologic findings do not completely explain the cutaneous patterns noted, and the patterns themselves do not represent simple infections of the skin. The micro-organisms found in culture of material from the lesions are those frequently found on normal skin or in other types of cutaneous infections which respond readily to antiseptic and antibiotic therapy. The entire skin of a patient so afflicted may be hypersensitive. At times, under such conditions, even hypodermic injections will initiate an ulcerative process. Additional evidence of this allergic nature may be noted in the episodes of episcleritis which may occur. Sensitivity to drugs may be present, as was noted in case 1, with exacerbations of cutaneous lesions by phthalylsulfathiazole, and as occurred in case 3, with episodes of fever associated with the ingestion of carbarsone.

7. Warner, W. P.: A Case of Ulcerative Colitis, in a Child, Associated with a Bullous Skin Eruption, Canad. M. A. J. **18**:571-573 (May) 1928.

8. Cole, H. N., and Driver, J. R.: Dermatitis Vegetans, Arch. Dermat. & Syph. **35**:743-744 (April) 1937.

9. Goldsmith, W. N.: A Case of Pyodermite végétante (Hallopeau), Brit. J. Dermat. **53**:299-318 (Nov.) 1941.

10. Heisel, E. B., and Krause, M. E.: Pemphigus Vegetans, Arch. Dermat. & Syph. **45**:606-607 (March) 1942.

More than 40 reports of cases of dermatitis vegetans and pemphigus vegetans have been published in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY since 1920. No mention is made of chronic ulcerative colitis in association with these conditions.

SUMMARY

Five cases of vegetating, pyogenic recalcitrant dermatoses complicating chronic ulcerative colitis are presented. Although the dermatoses manifested a clinical resemblance to other types of vegetative dermatoses, especially pemphigus vegetans and *pyodermite végétante* (Hallopeau), they were distinguished by the fact that chronic ulcerative colitis was found to be an etiologic factor common to all the cases. An allergic reaction to drugs was established in one instance. Improvement of the patient's general health and control of the colitis are of fundamental importance in treatment.

TROPICAL ANHIDROTIC ASTHENIA

Thermogenic Anhidrosis

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IN 1944, Wolkin, Goodman and Kelley [1] described a new syndrome when they reported 8 cases of failure of the sweat mechanism. The patients, observed in an Army camp situated in the California desert, presented a typical history that did not conform to that of either heat stroke or heat exhaustion. The symptoms were associated with, or preceded by a period of excessive sweating, and, usually, some degree of prickly heat; then a cessation of sweating occurred over the entire body below the neck, with an outpouring of sweat from the face and neck. The systemic symptoms were generalized weakness, exhaustion, sensation of body warmth, dizziness, headache, palpitation and rapid respiration. The objective findings were warm, dry skin from the neck down, with profuse sweating of the face and neck. There was a generalized, fine papular eruption resembling goose flesh, and in cases of longer duration there was a fine, branny desquamation. All the patients improved in a cooler environment and the condition returned to normal within a few weeks. The starch-iodine test of Minor gave negative results over the body. Sweat stimulation could not be produced with pilocarpine or methacholine (acetylbetamethylcholine) except on the face and neck; salt solution administered intravenously or orally gave no relief. Exercise or exposure to sunlight reproduced all the symptoms. After the return of a normal sweating pattern, the symptoms were not reproduced by exercise.

Several writers discussed this new syndrome, attempting to clarify its cause [2]; shortly after the original publication, articles appeared reporting similar cases from all over the world. Allen and O'Brien [3]

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1. Wolkin, J.; Goodman, J. I., and Kelley, W. E.: Failure of the Sweat Mechanism in the Desert, J. A. M. A. **124**:478 (Feb. 19) 1944.

2. Miller, M. M.; Silverman, J. J., and Powell, V. E.: Failure of the Sweat Mechanism in the Desert, Correspondence, J. A. M. A. **124**:1152 (April 15) 1944. Blank, H.: Anhidrosis Following Exposure to Extreme Heat, Correspondence, ibid. **124**:1152 (April 15) 1944. Novy, F. G., and Ramsey, J. H.: Failure of the Sweat Mechanism in the Desert, Correspondence, ibid. **125**:738 (July 8) 1944.

3. Allen, S. D., and O'Brien, J. P.: Tropical Anhidrotic Asthenia, M. J. Australia **2**:335 (Sept. 23) 1944.

recorded 22 cases occurring in New Guinea and Northern Australia. All the patients had previously had an extensive prickly heat, which had disappeared two to four weeks before the absence of sweating was observed. The symptoms of exhaustion, dyspnea, palpitation, headache and giddiness began insidiously, were first noticed during the heat of the day and were increased by exercise; relief was obtained by rest in a cool place. Some patients had an elevation of tempertaure to 102 F., a pulse rate of 140, and a respiratory rate of 46, per minute, with the characteristic profuse sweating of the face, head and neck. At times patients were observed with moisture of the palms, soles and axillas; elsewhere, however, the skin was dry, rough and inelastic, with an exaggerated goose flesh appearance, the eruption being made up of many grayish white papules not associated with the hair follicles, and from which a drop of fluid could be obtained when pricked.

Extensive histologic studies were made of serial sections of the skin; most of the changes occurred in the sweat glands and their ducts and consisted in the following picture: (1) occlusion of the mouth of the sweat gland duct by a minute plug consisting of keratin and cells; (2) formation of a small vesicle in the malpighian layer by cystic distention of the occluded duct, which sometimes was ruptured; (3) lymphocytic infiltration and dilatation of lymphatics around the ducts immediately below the vesicle, in the papillary layer of the dermis; (4) dilatation of the whole lumen of the dermal part of the duct to two or three times its normal size; (5) moderate distention of the acini of the sweat glands, with some degree of distortion and atrophy of the secreting cells; (6) accumulation of tissue fluid in the tissue spaces of the dermis and dilatation of the lymphatics, especially around the sweat glands and their ducts; (7) slight degree of vascular congestion; (8) blockage of hair follicles by a layer of keratin, resulting in distention of the follicles with sebum and atrophy of the hairs.

From this important study, it was concluded that the basic cause of the histologic changes was the hyperkeratosis which occluded the ducts, and that the sweat was still formed but could not reach the surface of the skin. After rupture of the ducts, the sweat was reabsorbed by the lymphatics and carried to the regional glands, which became enlarged. These histologic studies revealed a constant, minute hyperkeratotic area structurally confined to and surrounding the sweat gland duct. The opening of the duct was completely occluded by concentric lamellas of keratin, the result of the preceding miliaria rubra. Sweat was formed but was reabsorbed into the lymphatic system. There was suppression of sweat, rather than primary failure of secretion.

Ladell, Waterlow and Hudson [4] studied 55 cases in southern Iraq which were similar to those previously reported; the anhidrosis was preceded by extensive miliaria, followed by a desquamating stage and gradual recovery. They expressed the belief that the cause of this condition was (1) fatigue of the sweat glands from prolonged overactivity; (2) failure of the controlling mechanisms, either central or peripheral, or (3) pathologic changes interfering with the function of the glands.

Since these early reports, thermogenic anhidrosis has been observed in all parts of the world, both in hot, dry climates and in hot, humid climates; and cases have been reported from California, Louisiana, Texas, Ohio, South Pacific, New Guinea, Australia, North Africa and Iraq. Goodman [5] expressed the opinion that this condition would very likely be the commonest of the manifestations associated with excessive heat.

In normal persons, sweating is initiated physiologically whenever the external temperature reaches a point at which the need for body heat dissipation exists. There is a thermoregulatory mechanism controlled by the autonomic nervous system in relation to the thermoregulatory center in the hypothalamus. Control of sweating may be central, by the hypothalamus, or peripheral, by the nerve ends of the sweat glands. A disturbance of central control would not be likely to exempt the face and neck. Observations of this effect in cases of injury and cerebral operative procedures show complete loss of sweating. At times, cranial anomalies, associated with local changes, occur, such as sweating on one side of the face. There is no evidence that sweating of the face and neck is separately controlled. It is known that sweat glands may function for long periods after complete denervation; contact sweating has been observed as long as two years after denervation.[6] The cholinergic drugs fail to produce sweating in such cases, indicating a local dysfunction of the glands, but these drugs also fail in cases of damage to the central nervous system. It has been suggested that excessive heat and overstimulation of the sweat glands for a period may produce fatigue of the thermoregulatory mechanism, resulting in a temporary functional paralysis. Gerking and Robinson [7] observed a decrease in sweating in men working in extreme heat and concluded that in some

4. Ladell, W. S. S.; Waterlow, J. C., and Hudson, M. F.: Desert Climate: Physiological and Clinical Observations, Lancet **2**:491 (Oct. 14); 527 (Oct. 21) 1944.

5. Goodman, J. I.: Personal communication to the author.

6. Hyndman, O. R., and Wolkin, J.: Sweat Mechanism in Man: Study of Distribution of Sweat Fibers from Sympathetic Ganglia, Spinal Roots, Spinal Cord and Common Carotid Artery, Arch. Neurol. & Psychiat. **45**:446 (March) 1941; Pilocarpine Sweating Test: I. A Valid Indicator in Differentiation of Preganglionic and Postganglionic Sympathectomy, ibid. **45**:992 (June) 1941.

(Footnotes continued on next page)

way the sweating mechanism becomes fatigued. Ladell [8] observed that the rate of sweating may be as high as 3 liters per hour, although such a rate is not maintained long because of fatigue of the sweat glands. This fatigue was compared with the reduction in response in many other organs which follows long-continued stimulation.

Cases of generalized acquired anhidrosis have been reported; recently Engelhardt and Melvin [9] reported a case of anhidrosis of thirteen years' duration which developed after the patient fainted while scrubbing floors, and cited 2 cases in which the condition followed typhus and typhoid. Congenital cases have been observed for many years and described under the title of congenital ectodermal dysplasia of the anhidrotic type. In such cases there is usually a reduction in the number or an absence of sweat glands, and the group probably includes many instances of intolerance to heat and exercise and some of the obscure cases of fever in warm weather and fever associated with certain occupations.

Strauch [10] presented a case of anhidrosis before the Cleveland Dermatological Society in which there was profuse sweating of the face, neck, hands and feet and slight sweating in the axillas and inguinal regions; all other areas of the body remained exceptionally dry. Heating by an electric blanket failed to produce sweating over the body, and nausea and dizziness developed. Exercise or exposure to sun produced abnormal sweating of the face, hands and feet, as well as headache, dizziness, palpitation, nausea and weakness. Starch-iodine tests gave negative results; methacholine bromide produced no sweating in the areas of dryness. In most of the cases previously reported, there had been a return to normal within two to three months, whereas in Strauch's case all the normal symptoms were present at the end of eighteen months.

Sulzberger, Emik and Zimmerman [11] reported on their studies of miliaria rubra (prickly heat), in which they observed histologic changes identical with those reported by Allen and O'Brien [3] and confirmatory of those described by Pollitzer.[12] They noted that there was an absence of sweating which might persist for weeks after the inflammatory phase

7. Gerking, S. D., and Robinson, S.: Decline in the Rates of Sweating of Men Working in Severe Heat, Federation Proc. **5**:32 (Feb.) 1946.

8. Ladell, W. S. S.: Thermal Sweating, Brit. M. Bull. **3**:175, 1945.

9. Engelhardt, H. T., and Melvin, J. P., Jr.: General Acquired Anhydrosis, Am. J. M. Sc. **210**:323 (Sept.) 1945.

10. Strauch, J. H.: Acquired Generalized Anhidrosis with Localized Hyperhidrosis, Arch. Dermat. & Syph. **53**:70 (Jan.) 1946.

11. (*a*) Sulzberger, M. B., and Emik, O.: Studies on Prickly Heat: I. Clinical and Statistical Findings, J. Invest. Dermat. **7**:53 (Feb.) 1946. (*b*) Sulzberger, M. B., and Zimmerman, H. M.: Studies on Prickly Heat: II. Experimental and Histologic Findings, ibid. **7**:61 (Feb.) 1946.

12. Pollitzer, S.: Prickly Heat, J. Cutan. Dis. **11**:50, 1893.

of prickly heat had subsided and that these zones of inhibited sweating might enlarge and extend. They advanced the hypothesis that continuous profuse sweating leads to maceration of the cutaneous surface, faulty keratinization, occlusion of the sweat pores by horny plugs and irritation of the tissue by substances derived from the concentration of retained sweat in the orifices and superficial ducts, the causal chain of events in prickly heat. Attention was called to the similarities between this process in the sudoriferous apparatus and the process in the sebaceous structures which is recognized as causing acne. Sulzberger, Emik and Zimmerman expressed the opinion that the syndrome described as tropical anhidrotic asthenia may be an ultimate state in cases of widespread or generalized eruptions of miliaria. The similarity between the histologic picture of prickly heat and that of tropical anhidrotic asthenia supports this contention.

Sulzberger, Zimmerman and Emerson [13] observed a case of thermogenic anhidrosis in which physiologic, biochemical and histologic studies were carried out. Their histologic studies confirmed the earlier work of Allen and O'Brien that the plugging of the sweat ducts and their orifices probably plays a fundamental part in the disease process. Their investigation indicates that in this condition there is a faulty keratinization with the formation of the parakeratotic and hyperkeratotic plugs. They stated the belief that superficial obstruction of the sweat ducts by the horny plugs plays an important role in the causation of anhidrotic asthenia and that thermogenic anhidrosis is to be regarded as a sequela of severe, extensive prickly heat, or at least as the result of some fundamental process producing occlusion of the sweat gland openings, with failure of the sweat to reach the surface and cool by evaporating.

Shortly after the original publication, I observed my first case of this condition, that of a young Marine who did patrol duty in a tank during the day and, of necessity, slept in the tank at night. There had been a period of excessive perspiration, with some prickly heat, and then the gradual development of systemic symptoms during the heat of the day and on exertion. These symptoms—weakness, exhaustion, sensation of warmth, dizziness, headache, palpitation, rapid respiration—progressed until he was no longer able to continue his duties. He was first observed a week later, on his evacuation to an adjacent hospital; at that time there was extensive generalized dryness, with a few fine papules over the body. Exertion produced warmth of the body, profuse sweating of the head and neck, an increase in respiratory and pulse rates and elevation of temperature and blood pressure. On his remaining in bed in a cool environment and with frequent cool showers, he was comfortable, and his symptoms gradually subsided. There was less noticeable exhaustion, and after four weeks he could walk briskly and, later, run a few hundred feet before the symptoms were reproduced. At the end of six weeks, normal activities did not produce symptoms, and there was a

13. Sulzberger, M. B.; Zimmerman, H. M., and Emerson, K., Jr.: Tropical Anhidrotic Asthenia (Thermogenic Anhidrosis) and Its Relationship to Prickly Heat, J. Invest. Dermat. **7**:153 (Aug.) 1946.

beginning return of perspiration over the body. The elevation of temperature, respiratory rate, pulse rate and blood pressure was not so great as previously observed. The patient's condition had returned almost to normal at the end of six weeks, when his transfer prevented further observation.

Three additional patients, all presenting the classic symptoms of the condition, were observed, and each, over a period of three to five weeks, with rest in a cool environment, made complete recovery. In 1 patient extreme, persistent pruritus was observed, even after all other symptoms had subsided.

During the past year, there was an opportunity to observe a case of thermogenic anhidrosis which had persisted for two years. A white man aged 24 first became ill while in New Guinea, in May 1944. There developed dryness, scaling and peeling of the palms and soles, which gradually increased to involve the entire body with a generalized exfoliative dermatitis. Numerous hyperkeratotic lesions developed over the palms and soles and about the feet and hands, and a few appeared elsewhere over the body. During the height of the dermatitis he noticed that the entire body was dry, without any evidence of perspiration, and that there was excessive perspiration about the face and neck. This condition persisted after the improvement of his exfoliative dermatitis and the disappearance of most of the hyperkeratotic lesions, for which he was hospitalized a year. He was discharged from the Army in February 1945 and during the following winter was able to work as a bus driver; but during the summer of 1946 he experienced exhaustion, dizziness, headache and palpitation on exertion. In August 1946, after a walk of three blocks, he had a temperature of 100.2 F., a respiratory rate of 36, and a pulse rate of 122, and profuse perspiration stood out in large drops over the forehead and cheeks. The entire skin of the body was warm and dry; there were mild desquamation, almost total absence of hair over the body and two large areas of hyperkeratosis over the palms. During his stay in Brooke General Hospital, from Aug. 5, 1944 to Feb. 9, 1945, the diagnoses were established as follows: (1) exfoliative dermatitis, generalized; (2) lichenoid dermatitis, with several histologic examinations of hyperkeratotic lesions revealing a process compatible with lichen planus (subsequent histologic examinations made by the Army Medical Museum resulted in a diagnosis of lichen planus hypertrophicus); (3) nephritis, chronic parenchymatous; (4) malarial fever, tertian, with demonstration of Plasmodium vivax, and (5) otitis externa.

This patient was again examined on Jan. 27, 1947, and since August 1946 there has been considerable improvement in the dryness and desquamation over his body and an increase in growth of the scalp hair, with some return of hair over the arms, chest and legs, although the body hair was still much less extensive than before his illness. The palms and soles were still dry and hyperkeratotic, and there were thick verrucous keratoses on each palm. Observation with several photographic lamps revealed excessive, profuse perspiration of the forehead, face and neck. The skin of the body became warm and was dry everywhere, with no perceptible perspiration. This patient, after having had a lichenoid dermatitis, with numerous hypertrophic lichen-planus-like lesions over the body, proceeding to a generalized exfoliative dermatitis, attained much improvement in a year, but at the end of two years had extensive anhidrosis. He continued to have systemic symptoms, particularly in warm weather, and during the summer of 1946 they were severe enough to incapacitate him from work. This case is similar to the one reported by Strauch, in which anhidrosis had been present for eighteen months.

The work of Allen and O'Brien [8] and Sulzberger, Zimmerman and Emerson [13] apparently indicates that the basic cause of the anhidrosis

is the hyperkeratoses which occlude the sweat gland ducts. There is histologic evidence that the glands continue to function but that the perspiration does not reach the surface and that the systemic symptoms are those of failure of the heat-regulatory mechanism. There is no decrease in the total production of sweat although it is produced in the limited area of the face and neck, but this limitation does interfere with body cooling, forcing increased respiration to help dissipate the heat. The accelerated respiration probably accounts for the dizziness, headache and palpitation and closely resembles the signs seen in the hyperventilation syndrome.

The observations of Sulzberger and Zimmerman on prickly heat are not entirely conclusive in some respects, even though there is histologic proof of obstruction of the sweat gland ducts. There probably is a decrease in perspiration associated with prickly heat, as the inflammatory lesions develop and obstruct the orifices, but all who have had experience in tropical climates and in the southern part of the United States know that the areas in which miliaria develops, are those in which there is continued excessive perspiration for a long period. The papules represent an inflammatory change at the duct orifices, which become obstructed, as originally described by Pollitzer in 1893 and recently confirmed by Allen, O'Brien and Sulzberger. However, it is improbable that the sweat gland ducts (approximately 1,000 per square centimeter, or 2,000,000 over the entire body surface) become obstructed by these keratotic plugs. This action is not a requisite of miliaria, but is essential to the theory of the role of mechanical obstruction in thermogenic anhidrosis. It is unlikely that the duct orifices would be uniformly obstructed in such a manner as to produce the sharply demarcated areas of dryess over the body with excessive perspiration about the face and neck. It is true that miliaria is observed less frequently about the face and neck, except for the forehead and beneath the chin, but in no case has there been absence of perspiration about the face and neck. It was constantly observed in the South Pacific that patients who had severe prickly heat had more lesions on the uncovered than the covered portion of the body, and that many times, the wearing of an undershirt improved or prevented prickly heat on the chest, back and abdomen. Sulzberger stated:

> The possible importance of these findings in relation to the pathogenesis of tropical anhidrotic asthenia is obvious. Should a sufficient number of available sweat pores become occluded as a result of extensive eruptions of prickly heat, this would, in our opinion, suffice to produce the manifestations of the syndrome known as tropical anhidrotic asthenia.

At present there is still no conclusive evidence of the underlying pathologic process producing thermogenic anhidrosis; it may be a defect of the thermoregulatory mechanism of the hypothalmus produced by

exposure to excessive heat, with failure of the central mechanism. However, in this instance there is no adequate explanation for the excessive perspiration of the face and neck. There is evidence that this condition may represent an abnormality in peripheral control, chiefly one of fatigue after excessive stimulation of the sweat glands, which, after a prolonged period, actually cease to function. This hypothesis is not confirmed by histologic examination, since there is evidence of dilatation of the ducts and the perspiration simply does not reach the surface and control body temperature by evaporation. There is no doubt a fault in the process of keratinization, which may be the significant factor in initiating the formation of hyperkeratotic plugs, with obstruction of the sweat gland ducts. However, it is difficult to comprehend the actual obstruction of hundreds of thousands of individual sweat glands on a purely mechanical basis. It seems therefore that a more fundamental pathogenesis exists in this disease process: a disturbance in the physiology of the skin, which relates either to fatigue following overproduction of organ function or, more likely, to a pathophysiologic disturbance in keratinization, which may have a relation to vitamin A deficiency, such as is thought to occur in the pilosebaceous apparatus involved in the production of acne. Changes in the pilosebaceous structure were observed by Allen and O'Brien.

SUMMARY AND CONCLUSIONS

The literature of the new syndrome thermogenic anhidrosis is reviewed.

This condition has been observed throughout the civilized world.

The significant process is a defect of keratinization, with the production of hyperkeratotic plugs which obstruct the sweat gland ducts.

The systemic manifestations occur as a result of changes in thermoregulation, with attempts at dissipation of heat by increased respiration.

It is difficult to visualize the individual, purely mechanical obstruction of hundreds of thousands of sweat gland duct orifices, with the usually rapid return of sweating in a cool environment; this apparatus failure may represent an organ which rebels at further activity after prolonged, excessive overproduction of secretion.

Some fundamental pathologic process of systemic origin must produce this syndrome, but it is probably unrelated to control of sweating by either the central or the peripheral nervous system.

This condition probably represents a systemic disturbance which interferes with keratinization, whether related to enzymes, vitamins or some other physiologic factor.

Further investigation of this new syndrome will be necessary before the pathogenesis can be completely determined.

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TREATMENT OF CUTANEOUS BLASTOMAS AND OTHER DISEASES WITH NITROGEN MUSTARD

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IT IS IMPORTANT that persons connected with all phases of medicine interest themselves in the study and application of new drugs and chemicals, particularly when allied diseases of the various specialties may be benefited by them. Nitrogen mustard is a relatively new chemical so far as its therapeutic and biologic actions in diseases, as first reported by Gilman and Philips,[1] are concerned. An official statement of its merits was made by Rhoads.[2] Both of these writers thoroughly discussed its chemistry and modes of action, and so further reference to this phase of the chemical will not be made. Though it is more than likely that numerous persons have treated cutaneous blastomas and other diseases with nitrogen mustard, there are only a few reports in the literature at this time. For that reason it was felt that the present report might be of interest.

Henstell and Tober[3] treated a 67 year old woman in November 1946 with nitrogen mustard (methyl-bis [2-chloroethyl]amine hydrochloride) dissolved in 5 cc. of distilled water injected into the tubing of an infusion of an isotonic solution of sodium chloride given intravenously; the same dose was repeated on two successive days. These authors stated that there was a prompt response to therapy and that the papules, patches of infiltration and pruritis began to disappear by the fourth day after treatment had been started. Nine days after treatment a specimen of the skin was taken for biopsy, and the pathologic report stated that "the intense infiltrate of earlier sections is

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1. Gilman, A., and Philips, F. S.: The Biological Actions and Therapeutic Applications of the B-Chloroethyl Amines and Sulfides, Science **103**:409-415, 1946.

2. Rhoads, C. P.: Nitrogen Mustards in the Treatment of Neoplastic Disease: Official Statement, J. A. M. A. **131**:656-658 (June 22) 1946.

3. Henstell, H. H., and Tober, J. N.: Treatment of Mycosis Fungoides with Nitrogen Mustard, J. Invest. Dermat. **8**:183-188, 1947.

gone." Since that time reports by Kierland, Watkins and Shullenberger,[4] Philpott, Woodburne and Waldriff[5] and Osborne, Jordan, Hoak and Pschierer[6] have appeared. In all these writings there has been a uniformity of opinion regarding nitrogen mustard in treatment of mycosis fungoides:

1. The drug is administered intravenously, and the routine dose should not exceed 0.1 mg. per kilogram of body weight. This dose should be repeated on three successive days.

2. Within four hours after the injection an effect on the gastrointestinal system is usually apparent, being manifested by nausea and vomiting, which is seldom prolonged. Kierland and associates stated that pyridoxine administered intravenously seemed of some value in decreasing the severity of nausea and vomiting.

3. There is usually a reflection of the cytotoxic action of the nitrogen mustard on the formed elements of the blood within the first six days of treatment. This results in lymphopenia, granulocytopenia, thrombocytopenia or a form of anemia, usually in the order named. Osborne and associates further stated that bleeding from the gums and purpuric lesions of the skin may occur.

4. Nitrogen mustard is extremely effective in causing involution of infiltrative plaques, tumors and erythroderma and in controlling the often associated severe and annoying pruritus. The latter effect usually does not last longer than from three to five months. The relief from pruritus is no more lasting than that following roentgen irradiation though it is much prompter.

5. In general, the interval between courses of nitrogen mustard should not be less than from six to eight weeks, if blood dyscrasias are to be avoided. This point was further stressed by Spurr in his discussion of Osborne's paper.

Henstell, Tober and Newman[7] reported 6 cases of mycosis fungoides treated with nitrogen mustard and stated that in each the patient showed striking and immediate response to the drug regardless of the type and stage of the disease. This response seemed to bear no relationship to resistance to roentgen rays. The number of courses

4. Kierland, R. R.; Watkins, C. H., and Shullenberger, C. C.: The Use of Nitrogen Mustard in the Treatment of Mycosis Fungoides, J. Invest. Dermat. **9**:195-203, 1947.

5. Philpott, O. S.; Woodburne, A. R., and Waldriff, G.: Nitrogen Mustard in the Treatment of Mycosis Fungoides, J. A. M. A. **135**:631-633 (Nov. 8) 1947.

6. Osborne, E. D.; Jordan, J. W.; Hoak, F. C., and Pschierer, F. J.: Nitrogen Mustard Therapy in Cutaneous Blastomatous Disease, J. A. M. A. **135**:1123-1128 (Dec. 27) 1947.

7. Henstell, H. H.; Tober, J. N., and Newman, B. A.: The Influence of Nitrogen Mustard on Mycosis Fungoides, Blood **2**:574-578, 1947.

had no effect on the final outcome of the disease, and each course appeared to be followed by short periods of improvement. These authors further stated that those patients whose biopsy specimens showed a high incidence of reticuloendothelial cells had the best response to therapy. This observation may be of value in prognosticating the various types of mycosis fungoides

The present study is of 6 patients, 3 having mycosis fungoides; 1, nonlipid histiocytosis, and 2, chronic resistant inveterate psoriasis vulgaris. All the patients in this series were treated with methyl-bis (2-chloroethyl)amine hydrochloride.

REPORT OF CASES

CASE 1.—The diagnosis was mycosis fungoides. A 74 year old white woman was referred to the dermatology clinic on Oct. 17, 1946, for a condition of the skin which had been present for five years. She stated that a small, itching lesion resembling ringworm had appeared on her face and that subsequently lesions had appeared on other portions of her body. She was admitted to the Cincinnati General Hospital, where the following observations were made. The patient was weak, poorly nourished and dehydrated and showed evidence of recent loss of weight. She was slightly confused and answered questions poorly. Various types of cutaneous lesions were noted: (*a*) papulosquamous, irregular plaques with sharply demarcated borders; (*b*) irregularly sized ulcers with necrotic bases; (*c*) deeply pigmented infiltrated plaques, and (*d*) foul-smelling, discharging tumors. The palms and soles were keratotic and edematous. Large lymph glands were present in the axillary and the inguinal areas. The distal portion of the tongue was beefy red, while the rest of it was dry and felt like sandpaper. The rest of the physical examination elicited no other positive findings. Biopsy specimens removed from the skin of the back and from a tumor showed the typical pathologic changes of mycosis fungoides. The patient was failing rapidly, and through the courtesy of Dr. Harold Schiro of the medical department she was given 5 mg. of nitrogen mustard in 5 cc. of saline solution intravenously on October 25 and for each of three successive days (0.1 mg. per kilogram of body weight). A sternal marrow puncture showed hyperplasia of the myeloid elements of the marrow. On the second day after nitrogen mustard was administered the patient became deeply jaundiced, and this manifestation increased up to the time of death, which occurred on October 29. It was noted on the fourth day after treatment with nitrogen mustard was started that a definite decrease had taken place in the size of the cutaneous lesions and tumors.

Postmortem Observations.—A postmortem examination on October 29, five hours after death, revealed the following gross anatomic changes: acute hepatic necrosis; pronounced icterus; lobular pneumonia; myocardial dilatation; pulmonary congestion and edema; hydrothorax; toxic nephrosis, and pulmonary emphysema. Observations in the microscopic examination were as follows: evidences of septicemia, focal pneumonia, acute bronchitis, mycosis fungoides with ulceration and secondary inflammation, focal necrosis of the liver, tubular degeneration of the adrenal glands, reticuloendotheliosis of the spleen and lymph nodes, slight acute ileitis, toxic nephrosis, chronic intrahepatic pericholangitis, slight chronic perihepatitis, slight toxic myocarditis, generalized vascular sclerosis, slight myocardial fibrosis, slight pulmonary emphysema and leiomyoma of the uterus.

Comment.—It is to be noted that in this particular case jaundice appeared on the second day of nitrogen mustard therapy and that at necropsy acute hepatic necrosis was a major diagnosis. On the other hand, in case 3 of Osborne's report jaundice cleared after treatment with nitrogen mustard. We believe that in our case nitrogen mustard was the cause of the acute hepatic necrosis. Furthermore, the postmortem findings failed to reveal metastatic or visceral infiltration of mycosis fungoides.

CASE 2.—The diagnosis was mycosis fungoides. A 64 year old Negro stated that his present illness had begun in 1942, when he had acquired a generalized scaling eruption which had been diagnosed by his attending physician as psoriasis. These lesions became more widespread and wept. The patient was first seen in the Cincinnati General Hospital in 1945, when he presented a diffusely distributed, hyperpigmented scaling eruption of the trunk, face and extremities. In a biopsy specimen of the skin taken at that time hyperkeratosis, appreciable parakeratosis and lymphocytic infiltrate extending throughout the cutis and papillary areas were seen. A diagnosis of mycosis fungoides was strongly considered but not proved at that time. The patient was treated with superficial roentgen therapy and did fairly well until March 1947, when he was admitted to the hospital because of recurrence of his eruption. At that time the dermatitis was more widespread, and hyperpigmented, indurated plaques were seen. Between these slightly elevated plaques universal scaling was present, and vegetating tumors were seen on the lower extremities. In biopsy of the plaques and the tumors a polymorphic infiltrate of the outer corium, typical of the pathologic changes seen in mycosis fungoides, was observed.

A dose of 7.0 mg. (0.1 mg. per kilogram of body weight) of nitrogen mustard was given intravenously on each of four successive days. The patient experienced some nausea and vomiting, which lasted from two to four hours after each injection. Four days after the last injection the verrucous lesions of the lower legs became necrotic and sloughed. Six days after treatment the leukocyte count fell from 4,900 to 3,600, with definite diminution of the lymphocytes.

Within two weeks the hemogram was again normal. Six weeks later another four day course of nitrogen mustard was given because of a recurrence of verrucous lesions on the extremities. This time the leukocyte count fell to 3,000, with the same diminution in lymphocytes. Two weeks later the hemogram was again normal. The skin showed pronounced improvement, and the patient was discharged from the hospital after his second course of nitrogen mustard treatment. Biopsy specimens of the skin taken before, during and after nitrogen mustard therapy showed no remarkable changes in the amount and character of the dermal infiltration. The patient returned two months later with a recurrence of his cutaneous lesions and was given a third course of nitrogen mustard therapy similar to that above. Again, he improved and was discharged two weeks after the completion of therapy. His last admission was in November 1947, four months after the third course of nitrogen mustard therapy, at which time the cutaneous changes that were present were more pronounced than those seen in any previous examination. He also presented ascites and edema of the lower legs and was placed under treatment with bed rest and digitalization, with some decrease in the edema of the legs. A paracentesis was done and 2,400 cc. of straw-colored fluid, which had a specific gravity of 1.008, was obtained. Biopsy of the liver revealed focal fatty vacuolization. At this time the patient was given sodium

para-aminobenzoate, 2 Gm. by mouth every two hours during his waking hours. This treatment definitely relieved the pruritus and healed all his ulcers. Three weeks after this treatment was started a blood count revealed 5 Gm. of hemoglobin, and use of the drug was immediately stopped. A transfusion restored the hemoglobin level. The patient's condition became steadily worse, and he died on Jan. 29, 1948. Permission for necropsy was denied.

Comment.—This patient received three courses of nitrogen mustard therapy and had an initial response after each course of treatment. However, the effects were of short duration. Despite therapy and the good clinical response the microscopic infiltrative reaction was never altered. During each course of nitrogen mustard therapy the patient experienced gastrointestinal upsets, and shortly after therapy the hemogram revealed a decrease in leukocytes, particularly lymphocytes. Sodium para-aminobenzoate was given for three weeks, with a dramatic healing of all the ulcers and control of the pruritus. The dosage was 2 Gm. every two hours. The patient must be carefully watched while being treated with this drug because of changes that may occur in the hemogram. In this instance there was an appreciable reduction in hemoglobin and red cells. We believe that sodium para-aminobenzoate warrants further trial.

CASE 3.—The diagnosis was mycosis fungoides. The patient, a 49 year old Negro man, was first admitted to the Cincinnati General Hospital in February 1946 for cellulitis and thrombophlebitis of the leg. He gave a history of generalized pruritis of six months' duration. His skin showed no primary lesions, and he was treated with bland antipruritic lotions and discharged, with improvement. He was readmitted in May 1947 because of severe generalized pruritus which had persisted for the past sixteen months. At this time the skin showed a universal desquamation with pronounced excoriations. Generalized adenopathy was present. In biopsy of a specimen from the right epitrochlear lymph node hyperplasia of the lymphoid tissue was seen, but there was no evidence of a malignant process. A biopsy specimen of a hyperpigmented area of the skin revealed hyperkeratosis, acanthosis and a diffuse polymorphic cellular infiltrate of the outer corium, thought to be diagnostic of mycosis fungoides.

The patient was treated with nitrogen mustard, 8.3 mg. (0.1 mg. per kilogram of body weight) administered intravenously every day for four successive days. Two days after therapy had begun the leukocyte count dropped from 6,500, with 78 per cent neutrophils and 14 per cent lymphocytes, to 2,600, with 50 per cent neutrophils and 17 per cent lymphocytes. It promptly returned to normal within two weeks after treatment. The patient's pruritus and desquamation subsided, and he was discharged (much improved) two weeks after nitrogen mustard therapy. The comparison of biopsy specimens taken before, during and after nitrogen mustard therapy revealed no microscopic changes in the infiltration of the cutis.

The patient's clinical improvement was of short duration, and he was readmitted to the hospital because of similar complaints of pruritus eight weeks later. Examination of the skin revealed dryness, thickening and generalized scaling, associated with pronounced excoriations. Biopsy of an inguinal node revealed a nonspecific subacute and chronic inflammatory reaction. Laboratory examinations consisted of tests for hepatic function, urinalysis, determinations of total plasma

proteins and of blood urea nitrogen and blood serologic tests, in all of which the findings were normal. The patient was retreated with nitrogen mustard in the same manner and dose as before. There was prompt relief of the pruritus, and the skin showed clinical improvement. The patient, much improved, was discharged from the Cincinnati General Hospital on October 28, this date being the last time we saw him.

Comment.—This case again demonstrates the fact that, despite clinical improvement after each course of nitrogen mustard therapy, there was no change observed in the microscopic examination of the skin. The period of improvement following each course of nitrogen mustard was of short duration, and the shortest possible time elapsed between the first and the second treatment. There was a prompt drop in white cells after therapy, with a return to normal two weeks later.

CASE 4.—The diagnosis was nonlipid histiocytosis. The patient was a 15 year old white girl, admitted to the Cincinnati General Hospital on March 31, 1947. Her present illness had begun sixteen months previously when enlargement and tenderness of the submaxillary nodes had developed shortly after an infection of the upper respiratory tract. Subsequently similar manifestations appeared over the scalp. Roentgenograms showed areas of rarefaction in the skull. The lesions of the scalp and the submaxillary area broke down and drained. For this development the patient was given roentgen therapy over the lesions, with temporary improvement The patient had noticed brownish spots appearing on her face, neck and chest for the past year.

Clinical Examination.—An examination at the hospital revealed an emaciated, pallid girl with numerous, 2 to 3 mm., maculopapular brownish lesions scattered over the forehead, face and neck. Two soft, bluish tumors were present beneath the ear. A large swelling over the right parietal area of the scalp was crusted and exuded purulent material. A similar lesion was seen on the right side of the head. Three ulcers were present on the posterior portion of the left thigh and two on the right thigh. They were about 2 to 4 cm. in diameter. There were no other positive findings on physical examination. The blood chemistry was as follows: 126 mg. of cholesterol, 370 mg. of fatty acid in the serum and 5.98 Gm. of proteins per hundred cubic centimeters. The prothrombin time was 17 seconds (13 to 14 seconds), normal; there was 8.6 Gm. of hemoglobin, and the leukocyte count was 16,500, with 68 per cent neutrophils, 4 per cent eosinophils and 28 per cent lymphocytes.

Microscopic Examination.—On biopsy specimen of the lesion over the right mandible Dr. Edward Gall made the following observations:

"The lesion is much distorted as a result of superficial ulceration and infection of the granulation tissue. The striking feature is the presence of large numbers of multinucleated giant cells of the foreign body variety which are associated with variable numbers of macrophages, eosinophils and other components of granulation tissue. Brownish hemosiderin-like pigment is widely distributed and engulfed by component cells. The cytoplasm in many of the phagocytes is vacuolated, but unfortunately no material was preserved for fat stains. Special stains for iron show cells containing hemosiderin. The microscopic picture is consistent with nonlipid histiocytosis."

During her stay in the hospital the patient was found to have true diabetes insipidus. She was treated with large doses of penicillin and streptomycin,

without improvement. She was then treated with 4 mg. (0.1 mg. per kilogram of body weight) of nitrogen mustard once a day for four successive days. No improvement was noted in her general condition or in the local lesions. Her leukocyte count fell from 8,950, with 60 per cent neutrophils and 26 per cent lymphocytes, to 6,050, with 80 per cent neutrophils and 26 per cent lymphocytes. Her hemoglobin of 8 Gm. fell to 7 Gm. She was again treated with roentgen therapy, and the cutaneous lesions showed favorable response. Since her discharge from the hospital on Feb. 2, 1948, her cutaneous lesions have enlarged, the anemia has increased in severity and her general condition has become graver.

Comment.—Roentgen therapy had a better effect than did nitrogen mustard therapy. However, despite all types of treatment the patient has been steadily growing worse. Subsequently this case was diagnosed as eosinophilic granuloma of the bone, with cutaneous manifestations.

CASE 5.—The diagnosis was psoriasis vulgaris. The patient was a 30 year old white man admitted to the hospital on July 30, 1947, because of intractable psoriasis vulgaris of twenty-two years' duration. On admission he was found to have a generalized guttate type of psoriasis in which little of the cutaneous surface was spared. The only treatment was 7.3 mg. (0.1 mg. per kilogram of body weight) of nitrogen mustard administered intravenously every day for four successive days. No improvement was seen in the cutaneous lesions after completion of therapy. The patient suffered no untoward reaction from the nitrogen mustard therapy, and his blood count was essentially unchanged.

CASE 6.—The diagnosis was psoriasis vulgaris. The patient was a 24 year old Negro woman with a history of an eruption of the arms, legs and trunk of five years' duration. Examination revealed numerous discrete, nummular lesions over the extensor surfaces of the extremities and the trunk. The lesions were covered with a heavy, silvery scale. A biopsy of one of these lesions was made, and the microscopic changes observed were consistent with the typical microscopic features of psoriasis vulgaris. The patient was given 4.6 mg. (0.1 mg. per kilogram of body weight) of nitrogen mustard every day for four successive days and no additional therapy. The eruption was unchanged. During the course of treatment the patient's leukocyte count dropped from 8,000, with 68 per cent neutrophils, to 2,400, with 63 per cent neutrophils. Within two weeks the blood count had returned to normal.

Comment.—Neither of the patients with psoriasis vulgaris showed any improvement after treatment with nitrogen mustard. This psoriatic response may be interpreted as further proof of the fact that cellular susceptibility to nitrogen mustard is related to the proliferative activity of the tissue.

SUMMARY AND CONCLUSIONS

We wish to emphasize further that treatment with present nitrogen mustard compounds does not cure cutaneous blastomatous disease, particularly mycosis fungoides, nonlipid histiocytosis or psoriasis vulgaris. We do believe, however, that it offers a symptomatic palliative

method of therapy and another therapeutic measure besides roentgen therapy, heretofore one of the few proved beneficial methods of treatment of mycosis fungoides. The initial treatment with nitrogen mustard is not as dangerous as has been previously emphasized, if one adheres to safe dosage schedules. Though one cannot predict the types of reactions that may take place, frequent examination of the blood elements should be made during and after treatment. Even though there is a decrease in many of the blood elements shortly after therapy, these elements appear to return to normal within two weeks after therapy has been concluded. In mycosis fungoides there is usually an immediate response to the first course of treatment with nitrogen mustard, with a demonstrable effective diminution in the erythroderma and plaque and tumor formation. The pruritus is readily controlled, and this improvement may last for a far longer period than does any change noted in the skin itself. Successive courses of treatment are of value but seem to show less and less temporary effect on the tumor and infiltration stage. Repeated courses of treatment do not appear to produce severe dyscrasias of the blood or greater changes in the blood elements than those noted in the initial course of treatment. In our cases of mycosis fungoides, nitrogen mustard therapy did not affect the microscopic infiltration in the cutis, as was substantiated by biopsy of specimens taken before, during and after therapy. This observation, however, may have been due to the fact that in our cases there was a lower incidence of reticuloendothelial cells, as demonstrated by Henstell and associates.

Nitrogen mustard has a more dramatic immediate effect on mycosis fungoides than has roentgen irradiation, but it offers no better prognosis. The preceding statement may be reversed with reference to nonlipid histiocytosis. Nitrogen mustard appears to be superior to irradiation in control of pruritus. Also, when no further irradiation can be given nitrogen mustard may still be administered. Although nitrogen mustard and irradiation have been given at the same time, as has been demonstrated by Henstell and associates, it appeared to us that this procedure might be followed by more deleterious effects on the blood elements.

Inasmuch as there is still too little evidence that nitrogen mustard is of definite, proved value in blastomatous disease, its application should still be controlled by a tumor committee in each hospital and this therapy should remain a hospital procedure. As was stated before, nitrogen mustard had no effect in involuting nonlipid histiocytosis or chronic inveterate psoriasis vulgaris. We should further like to make note of the fact that sodium para-aminobenzoate was used in the second case of mycosis fungoides, with prompt control of the pruritus and healing of the ulcers The hemogram should be carefully

studied while this drug is being used, and we believe that use of sodium para-aminobenzoate warrants further study in the treatment of mycosis fungoides or allied diseases.

Addendum.—Three other patients have been treated with nitrogen mustard under our supervision. A patient with Letterer-Siwe disease was treated at Children's Hospital, Cincinnati, without improvement. Dr. Adolph Loveman of Louisville, Ky., treated 2 patients, 1, with mycosis fungoides, with temporary improvement and the second, with a case of eosinophilic granuloma of bone and skin, with no results.

At the time of writing, the patient in case 3 is living and well.

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EXPERIMENTAL SYPHILIS IN THE GOLDEN HAMSTER

Failure to Transmit Infection by Coitus and from Syphilitic Parents to the Newborn

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A DIVERSITY of opinion still exists as to whether or not syphilis can be transmitted in the rabbit and the mouse by coitus and from syphilitic parents to the newborn. Levaditi [1] and his group have reported the development of dark field–positive genital lesions through mating a normal female rabbit with a male that had syphilitic lesions of the glans penis and the prepuce. Albrecht [2] also obtained successful transmissions of the disease from a syphilitic male to a normal female and found that the popliteal nodes of the female rabbit were infectious. The ability to induce symptomless syphilitic infection in male rabbits through cohabitation with females that had healed vulvar syphilomas was reported by Kolle [3] and by Finkelstein and Orlow.[4]

Failure to transmit syphilis in rabbits was reported by Fischl,[5] who in a large series found that no male rabbit with either early or late syphilis could infect a female rabbit through coitus. Similar results have been obtained by Gregoriev and Jarisheva [6] and by Kemp,[7] who

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Studies and contributions from the Department of Dermatology and Syphilology, University of Michigan Medical School, service of Dr. U. J. Wile and Dr. A. C. Curtis.

1. Levaditi, C.; Marie, A., and Isaicu, L.: Étude expérimentale de l'hérédité syphilitique, Compt. rend. Soc. de biol. **85**:342-343, 1921.

2. Albrecht, B.: Die vaginale symptomlose Syphilisinfektion des Kaninchens und ihre Uebertragung durch den Geschlechtsakt, Deutsche med. Wchnschr. **56**:93-95, 1930.

3. Kolle, W.: Die Bedeutung der experimentellen symptomlosen Syphilisinfektion für die Erforschung der Lues-Epidemiologie und Pathologie, Centralbl. f. Bakteriol. (Abt. 1) **106**:134-139, 1928.

4. Finkelstein, J. A., and Orlow, S. S.: Zur Frage der experimentellen kongenitalen Kaninchensyphilis, Dermat. Wchnschr. **92**:203-209, 1931.

5. Fischl, R.: Die experimentelle Erzeugung kongenitaler Syphilis, bisherige Erfahrungen and eigene Versuche, Med. Klin. **22**:1927-1928, 1926.

6. Gregoriev, P. S., and Jarisheva, D. G.: Uncommon Observation in the Experimental Study of Inherited Rabbit Syphilis, Urol. & Cutan. Rev. **32**:222-223, 1928.

7. Kemp, J. E.: The Infectiousness of the Semen of Rabbits with Late Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **26**:16-20, 1942.

stated that the semen of rabbits with late syphilis was either free from treponema or contained them in such small numbers that it was not infectious for the female. He demonstrated, moreover, that female rabbits in the control group were susceptible to intravaginal infection with a relatively small inoculum (one organism per four to five high power dark fields).

Newborn rabbits from matings in which one or both parents were syphilitic before coitus have shown no evidence of the disease by dark field examination, by organ transfers or by immunity to challenge inoculations with syphilitic material.[8] In isolated instances stigmas of syphilis have been observed. Inherited specific keratitis with positive reactions to the Wassermann test in rabbits born of syphilitic mothers has been reported.[6] Brown and Pearce [8a] observed abnormalities of the eyes, skin and hair in a litter born of syphilitic rabbits. Repeated instances of premature births of dead fetuses have been noted by Grigorieff [8d] and by others.[9]

Studies on the transfer of syphilitic infection by copulation in the mouse are few. Mulzer and Hahn [10] reported an instance in which a female mouse was infected following coitus with a syphilitic male. Proof of infection was determined by inoculation of a rabbit with an organ emulsion from the female mouse. Vaisman [11] failed to demonstrate

8. (*a*) Brown, W. H., and Pearce, L.: The Occurrence of Stigmata of Congenital Syphilis in Rabbits with Especial Reference to the Factor of Inheritance, J. Exper. Med. **41**:795-805, 1925. (*b*) Seiffert, W.: Experimentelle Untersuchungen über die Infektion mit Spir. pallida durch Kohabitation und durch die Plazenta, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:386-389, 1934. (*c*) Uhlenhuth, P., and Grossmann, H.: Untersuchungen zur Frage der "Vererbung" der experimentellen Kaninchensyphilis, Med. Klin. **23**:18-20, 1927. Kemp, J. E., and Rosahn, P. D.: Experimental Study of Congenital Syphilis, Including a Study of Infectiousness of Blood, Uterus, and Placenta of Pregnant Rabbits with Early Syphilis, Bull. Johns Hopkins Hosp. **60**:45-55, 1937. (*d*) Grigorieff, P.: Angeborene durch ein in die vordere Augenkammer infiziertes Kaninchen übertragene Syphilis, Dermat. Wchnschr. **89**:1122-1124, 1929. (*e*) Kemp, J. E., and Fitzgerald, E. M.: Studies in Experimental Congenital Syphilis and the Transference of Immunity from Immune Syphilitic Female Rabbits to Their Offspring, J. Invest. Dermat. **1**:353-365, 1938. Levaditi and Isaicu.[1] Finkelstein and Orlow.[4] Fischl.[5]

9. Brown, W. H., and Pearce, L.: On the Reaction of Pregnant and Lactating Females to Inoculation with Treponema Pallidum: A Preliminary Report, Am. J. Syph. **4**:593-597, 1920. Nyka, W.: Contribution à l'étude du mécanisme de la transmission de la syphilis de la mére a l'embryon chez la lapine et la souris, Compt. rend. Soc. de biol. **114**:1258-1260, 1933. Gregoriev and Jarisheva.[6]

10. Mulzer, P., and Hahn, C. F.: Zur experimentellen Mäuse- und Meerschweinchen-Syphilis, Arch. f. Hyg. **103**:95-106, 1930.

11. Vaisman, A.: La syphilis inapparente expérimentale chez la souris, Paris, Imp. Tancrede, 1936; cited by Gueft, B., and Rosahn, P. D.: Experimental Mouse Syphilis: A Critical Review of the Literature, Am. J. Syph., Gonor. & Ven. Dis. **32**:59-88, 1948.

sexual transmission of the disease in the mouse. Seiffert [8b] found that the placentas of mice were impermeable to syphilitic infection and that the young were never infected. Levaditi [12] reported that though the uterus, ovaries and testes of mice might harbor spirochetes, the disease was not transmitted to the newborn. Takahasi [13] also observed negative results when he attempted to obtain evidence of infection with congenital syphilis in mice that were infected either before or after impregnation and coupled with healthy or infected male animals. Since neither the rabbit nor the mouse has proved well adapted to the study of transmission of syphilis by coitus or congenitally from syphilitic parents to newborn, similar experiments were carried out in the golden hamster (Cricetus auratus Waterhouse).

MATERIAL AND METHODS

The dark field–positive testicles of a rabbit previously inoculated intratesticularly with the Nichols strain of Treponema pallidum were removed, ground and emulsified with the addition of 18 cc. of sterile isotonic sodium chloride solution. Four female and 4 male adult hamsters were inoculated intraperitoneally with 2 cc. of this emulsion. In a control rabbit inoculated intratesticularly with 1 cc. of the same emulsion, there developed dark field–positive lesions in thirty days, and the Kahn test elicited a positive reaction of 160 units. The major part of the experiments was carried out from October to the following April. The animals were kept in a warm room and fed on a complete mouse ration with supplementary greens and alfalfa.

EXPERIMENT 1.—A male and a female hamster were mated 30 days after inoculation. Seventeen days later there were 9 newborn. Twelve hours after birth, 6 of the litter were killed and an organ emulsion consisting of brains, spleens, hearts and lungs was prepared with 10 cc. of sterile isotonic sodium chloride solution. Three cubic centimeters of this emulsion was inoculated into each testicle of a rabbit, in which clinical or serologic evidence of syphilis failed to develop in 124 days. Later, a challenge inoculation into this rabbit produced a syphiloma in 37 days. One hamster of this litter was killed when 80 days old. An organ emulsion of all the organs was prepared and inoculated into a rabbit, which failed to contract syphilis in 111 days. Again, a subsequent inoculation was positive in 15 days. The remaining hamsters of the litter were inoculated intraperitoneally, when 80 days old, with dark field–positive rabbit material. Seventy days later these 2 animals were killed and a pooled organ emulsion of each hamster was prepared. In both rabbits inoculated with these two emulsions syphilitic lesion developed in 38 days, and the Kahn test elicited reactions of 20 and 320 units, respectively. Ninety days after the 2 parent hamsters had been

12. Levaditi, C.; Vaisman, A.; Schoen, R., and Manin, Y.: Tentatives de transmission héréditaire de l'infection syphilitique inapparente chez la souris blanche, Compt. rend. Soc. de biol. **118**:962-963, 1935.

13. Takahasi, H.: Experimentelle Untersuchungen über die angeborene Syphilis, Jap. J. Exper. Med. **16**:1-19, 1938.

inoculated, they were killed and an organ emulsion of each animal consisting of heart, brain, liver, spleen and gonads was prepared. In a rabbit inoculated with the male hamster emulsion there developed dark field–positive lesions in 33 days. The rabbit inoculated with material from the female hamster failed to manifest evidence of infection with syphilis in 104 days. Thorough dark field examinations of all the hamster material failed to reveal syphilitic lesions, and the young all appeared normal.

EXPERIMENT 2.—A normal adult female hamster and an adult male hamster which had been inoculated with active syphilitic material 30 days earlier were mated. Eighteen days later 9 young were born, of which 5 were killed when 6 hours old; a pooled organ emulsion was prepared. A rabbit that was inoculated intratesticularly with this preparation did not contract syphilis in 164 days. A challenge inoculation of dark field–positive syphilitic material into this rabbit revealed the development of positive lesions in 26 days.

Two hamsters of this same litter were killed when 38 days old. The organs of both animals were pooled, and an emulsion was prepared which, on inoculation into a rabbit, failed to cause syphilis in 106 days.

One littermate was killed when 80 days old. The organ emulsion of this hamster did not cause syphilis in a rabbit in 111 days. An emulsion prepared from the organs of the final littermate, which was inoculated with T. pallida when 80 days old and killed 68 days later, caused a syphiloma in a rabbit in 40 days. The father hamster was killed 89 days after inoculation with active syphilitic material. The organ emulsion of this animal caused a syphiloma in a rabbit in 23 days, with a positive reaction of 160 units to the Kahn test. The organ emulsion of the uninoculated female, killed 58 days after mating with the syphilitic male, failed to cause syphilis in a rabbit in 127 days. The challenge inoculation of the rabbit was positive in 24 days. The dark field examinations of the hamster material revealed normal conditions, and all the newborn appeared to be normal.

EXPERIMENT 3.—A male and a female hamster were mated 30 days after both had been inoculated with dark field-positive material from a syphilitic rabbit. Seventeen days later a litter was born, of which 2 were killed 6 hours after birth. A complete organ emulsion was made of these 2 newborn hamsters; it was inoculated into a rabbit, in which syphilis failed to develop in 161 days. A challenge inoculation of infectious material into this rabbit elicited a positive syphilitic response in 26 days. Three hamsters of this same litter were killed 18 days after birth, and a pooled organ emulsion of the 3 was prepared. Again, a rabbit inoculated with the emulsion prepared from the newborn hamsters failed to display a syphilitic orchitis in 150 days. The challenge inoculation was effective.

The mother hamster was killed 18 days after delivery, and her organ emulsion caused a syphiloma in a rabbit in 32 days. The father of the group was in early hibernation when it was killed, and its organ emulsion failed to cause syphilitic changes in a rabbit in 80 days. The challenge inoculation was positive in 15 days. The newborn were normal, and their emulsions were dark field–negative.

EXPERIMENT 4.—A female and a male hamster were mated 30 days after both had been inoculated with T. pallidum. The litter of 3 from this mating was not killed until 73 days old, when a pooled organ emulsion was made and inoculated intratesticularly into a rabbit; this animal failed to manifest evidence of syphilis in 110 days. The pooled organs of the father of this litter failed to cause a syphiloma in a rabbit in 112 days. The challenge inoculation was positive in 40 days. Inoculation of an organ emulsion of the mother hamster into a rabbit

caused a syphiloma in 30 days. The newborn hamsters appeared normal, and all dark field examinations of the hamster material failed to reveal syphilitic infection.

EXPERIMENT 5.—A syphilitic female hamster and a normal male hamster were mated. Twenty-eight days later a litter was born, of which 3 were killed when 24 hours old. The pooled organs of these 3 animals failed to cause a syphilitic orchitis in a rabbit in 136 days. One 55 day old hamster of this litter was inoculated with T. pallidum. It was killed 68 days later, and inoculation with the organ emulsion caused dark field–positive lesions in a rabbit in 40 days. An organ emulsion of the father failed to cause syphilitic changes in a rabbit in 80 days, while a similar emulsion of the organs of the mother caused a syphiloma in a rabbit in 28 days. Challenge inoculations into the rabbits in which syphilis did not develop were positive. The newborn hamsters manifested no abnormalities, and the dark field examinations of their organs did not reveal infection with syphilis.

To summarize these experiments, we find that inoculation with organ emulsions of hamsters born of syphilitic parents did not cause syphilitic changes in rabbits. This was true regardless of the age at which the young hamsters were killed. Emulsions of hamster siblings inoculated with T. pallidum caused syphilomas in rabbits. In no instance did the mating of a normal parent with an inoculated parent result in syphilitic changes in the normal mate as demonstrated by inoculations of organ emulsions into rabbits. In 2 of 4 instances in which an inoculated male hamster was mated with an inoculated female, inoculation with the organ emulsion of the male hamster failed to cause a syphilitic orchitis in a rabbit. This was also true with regard to 1 of the 4 inoculated female hamsters. All dark field examinations of hamster material gave negative results. Abnormalities in growth or body of the newborn hamsters were not observed. There was no suggestion that the course of the disease was milder in pregnant animals.

COMMENT

Results obtained with the hamsters in these experiments were much the same as those revealed in the major reports on experiments with the mouse and with the rabbit, in that the transmission of syphilis did not occur with coitus or pass from syphilitic parents to newborn animals. Immunity evidently was not present in the newborn, because the only instance in which inoculation with organ emulsions of the young hamsters caused syphilomas in rabbits occurred after the young had been inoculated with T. pallida. The failure of the organ emulsion of 2 of the inoculated parent males and 1 of the inoculated parent females to cause infection when it was inoculated into rabbits may have been due to hibernation of the hamsters. Bessemans and associates [14] found

14. Bessemans, A.; De Wilde, H., and de Moor, A.: Effet du sommeil hibernal sur la syphilis du hamster et du hérisson, Compt. rend. Soc. de biol. **129**:376-379, 1938.

that both the male and the female golden hamster may lose the syphilitic infection with normal hibernation but retain it with artificial hibernation. Jahnel [15] reported that other rodents such as the rellmouse and the European marmot act in a similar manner. Hibernation would seem to be the most likely cause for the failures to obtain infection in the adult syphilized hamsters in this experiment, because previously Wile and I [16] observed that syphilis was uniformly present in every syphilized hamster when the experiments were carried out in a different season of the year. However, if hibernation is the cause for the failures, it must not affect each individual hamster in the same way, since infection was found more often than not in syphilized hamsters.

SUMMARY

1. Healthy or syphilitic female hamsters were coupled with healthy or syphilitic male hamsters.

2. The newborn of such matings were not infected, as demonstrated by negative results with dark field examinations, by lack of immunity and by failure of organ emulsions from these animals to cause syphilomas when inoculated into rabbits.

3. In no instance did an infected hamster transmit the syphilis to a normal mate by copulation.

4. Inoculation with organ emulsions from 2 infected adult male hamsters and 1 infected adult female hamster failed to cause a syphilitic infection in a rabbit, probably because of hibernation of the hamsters.

15. Jahnel, F.: Further Studies in Experimental Syphilis: Efficacy of Natural Curative Factors, Am. J. Syph., Gonor. & Ven. Dis. **21**:18-31, 1937.

16. Wile, U. J., and Johnson, S. A. M.: Experimental Syphilis in the Golden Hamster, Am. J. Syph., Gonor. & Ven. Dis. **29**:418-422, 1945.

ORAL BISMUTH THERAPY IN DERMATOLOGY

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AND
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DETROIT

DURING the past twenty-five years bismuth has been employed extensively in the treatment of disease. It has proved an effective agent not only in syphilotherapy but also as an empiric remedy in a number of varied dermatoses, in the majority of which the etiologic basis has not been clearly established. Until recently, salts of bismuth have been administered by intramuscular injection and the results of oral administration of the drug have been disappointing, not because of a poor therapeutic response but because of gastrointestinal intolerance. Sodium bismuth triglycollamate (bistrimate®),[1] one of the newer bismuth salts available for oral administration, gives promise of being therapeutically effective without producing a high percentage of severe reactions. Gross and Wright [2] have reported satisfactory results from the use of this agent in the treatment of syphilis and a number of dermatoses known to be responsive to bismuth therapy. Sawicky [3] has also reported its use in 30 cases of chronic discoid lupus erythematosus. He concluded that it is at least as effective as parenteral bismuth.

Pascher, Sawicky, Silverberg and Emmet,[4] after a study of the results following the treatment of a group of miscellaneous dermatoses, concluded that sodium bismuth triglycollamate is a valuable therapeutic agent in the treatment of the discoid type of lupus erythematosus and that subjective or objective improvement was obtained in 40 per cent of the cases of lichen planus other than the hypertrophic form, in which the results were equivocal. They also concluded that the results in

1. Tablets were furnished by the Carroll Dunham Smith Pharmacal Company, New Brunswick, N. J.

2. Gross, E. R., and Wright, C. S.: Oral Bismuth Therapy in Syphilis and Various Dermatoses, read before the Pennsylvania Medical Society, Philadelphia, Oct. 8, 1946.

3. Sawicky, H. H.: Bistrimate (Sodium Bismuth Triglycollamate) Administered by Mouth in the Treatment of Chronic Discoid Lupus Erythematosus, J. Invest. Dermat. **9**:155 (Sept.) 1947.

4. Pascher, F.; Sawicky, H. H.; Silverberg, M. G., and Emmet, R.: Bistrimate for Lupus Erythematosus, Lichen Planus and Other Dermatoses, J. Invest. Dermat. **10**:441 (June) 1948.

3 cases each of granuloma annulare and scleroderma appeared to justify further therapeutic investigation.

PHARMACOLOGIC DATA

Sodium bismuth triglycollamate is formed by the combination of the bismuth salt of triglycollamic acid with three molar equivalents of disodium triglycollamate. It is water soluble without hydrolysis forming a solution which is approximately neutral in reaction and which is stable over the p_H range 2.8 to 10.0. Precipitation is not produced by phosphate or chloride ions normally found in body fluids.

One gram of the drug contains the equivalent of 0.138 Gm. of metallic bismuth and 0.823 Gm. of disodium triglycollamate.

The pharmacologic and toxicologic action of the drug has been investigated by R. A. Lehman and D. W. Fassett working in the Department of Therapeutics of the New York University College of Medicine. They concluded that it is a relatively nontoxic drug which is well tolerated in large doses over considerable periods of time and that triglycollamic acid does not participate in its toxic effects. Apparently the acute toxicity of the drug is primarily dependent on the total amount of bismuth absorbed.

In the work reported on here, sodium bismuth triglycollamate was used in treatment of several types of warts, condyloma acuminatum, lupus erythematosus, lichen planus and scleroderma. The cases were selected from those observed in private practice and from the outpatient department of dermatology of City of Detroit Receiving Hospital.[5] The drug was administered to adults in doses of one tablet (the equivalent of 75 mg. of metallic bismuth) three times a day after meals for three days, then two tablets three times a day after meals. The dosage was reduced in proportion to the age and weight of the patient. Additional therapy was not employed except as subsequently stated in a few instances. Those patients having positive blood serologic reactions for syphilis had all recived adequate syphilotherapy, and results of all blood counts and urinalyses were within normal limits.

Although the number of cases of oral bismuth therapy is not large and the results in some instances are not conclusive, it is believed that they are sufficiently satisfactory to warrant the further use of the drug.

VERRUCAE

Eighteen patients with various types of warts were treated with sodium bismuth triglycollamate. The group included 6 examples of juvenile flat warts in persons whose ages varied from 5 to 30 years.

5. From the Department of Dermatology and Syphilology, Wayne University College of Medicine, Loren W. Shaffer, M.D., Chairman.

Four were under 12 years of age and had typical lesions on the face and the dorsal surfaces of the hands. The duration varied from three to twelve months, and in all instances previous treatment, when given, had proved ineffectual. Unsuccessful forms of therapy included bismuth given intramuscularly, roentgenotherapy and local medication.

In all cases, the drug was administered in doses varying from two to six tablets a day and the duration of treatment varied from two to four weeks. One patient aged 5 years had complete involution of all lesions at the end of two weeks. In 2 patients aged 6 and 12 years with lesions on the forehead and dorsal surfaces of the hands complete involution was attained in one month. The remaining child, who was 7 years of age and had multiple lesions on the forehead, was completely freed of them at the end of three weeks. No additional therapy, except an antipruritic ointment in 1 instance, was given. There were no unfavorable reactions.

A woman aged 26 who had typical lesions of the face manifested no improvement after five weeks of treatment and the case was considered a therapeutic failure. Another woman aged 30 had complete involution of numerous lesions on the dorsal surfaces of the hands at the end of three weeks. Soreness of the gums developed, but treatment was not interrupted.

Four of 11 patients with verruca vulgaris were cured following a standard course of oral bismuth therapy averaging eight weeks in duration. Two of them had lesions which were limited to the nail folds, and in the light of previous experience with similar cases the results were particularly gratifying.

Five of the remaining patients manifested 75 to 90 per cent involution of lesions after treatment for five weeks. Their progress was satisfactory at the last observation, but the end result is, of course, unknown. In 2 instances no change was observed at the end of five weeks of treatment.

One patient with eleven plantar warts involving both soles exhibited no evidence of the lesions after six weeks of oral bismuth therapy, and there has been no recurrence of signs or symptoms after two months.

CONDYLOMA ACUMINATUM

Three patients with condyloma acuminatum were observed while on oral bismuth therapy. Although the number is small, it is believed that the results are worthy of recording.

A white woman aged 25 had a typical lesion attached to the left vaginal wall. It was approximately 7 cm. in diameter and protruded through the labia. The patient, when first observed, was seven months pregnant; the condyloma had first been noted five months previously. She was maintained on the standard dose of the bismuth preparation for a period of seven weeks without reaction.

At the end of that time the lesion was 1.5 cm. in diameter. Inasmuch as labor was imminent, treatment was discontinued. The patient was delivered of a normal male child without complication. She was unable to return for observation but was questioned by telephone four weeks after delivery and stated that the lesion was unchanged.

A white woman aged 49 was first examined because of a verrucous tumor 5 cm. in diameter and raised 2.5 cm. above the surface of the surrounding skin; the lesion was located in the left inguinal fold and had been present for five months. A biopsy specimen was reported to be condyloma acuminatum.[6] After twenty weeks of uninterrupted therapy with the bismuth preparation the tumor was 1 cm. in diameter; involution was evident only during the first fifteen weeks, the lesion remaining stationary during the last five weeks of treatment.

A Negro man aged 58 was seen because of condylomata acuminata which completely surrounded the anal orifice. The lesions extended about 3 cm. from the mucocutaneous junction. He had received oxophenarsine hydrochloride, intramuscular bismuth and penicillin for concomitant syphilis. He stated that the perianal lesions became more extensive during antisyphilitic therapy. During the first two weeks of treatment with bismuth sodium triglycollamate involution proceeded at a fairly rapid rate. It then became progressively lessened until the fourth month, after which further regression was not observed and treatment was discontinued. At that time approximately 15 per cent of the original lesion remained. A biopsy specimen obtained before the initiation of treatment confirmed the diagnosis.

LUPUS ERYTHEMATOSUS

Twelve patients with lupus erythematosus were observed while given oral bismuth therapy. In 9 the observations were clinically characteristic of the chronic discoid type, and in 8 this diagnosis was supported by examination of histologic sections. In 1 instance biopsy was not performed. In this group there were 6 women (5 Negro and 1 white) and 3 men (1 Negro and 2 white). Their ages varied from 27 to 65 years, the average being 46. In explanation of the preponderance of Negro patients, the majority were observed in an outpatient department where the patients are predominantly Negro.

The duration of the disease was less than nine months in 5 patients having the chronic discoid type of lupus erythematosus, and previous treatment had not been received in any instance. Additional treatment was not given except in 1 instance in which 5 per cent boric acid in a cold cream base was applied locally. Four patients have been under treatment for from three to twelve weeks. Improvement has been progressive in all cases as judged by cessation of symptoms (pain and/or pruritus), fading of erythema, flattening of the borders of the lesions and disappearance of scaling and follicular plugging. However, it was not considered that there was complete inactivity of the disease process, and it is, of course, problematic whether progress will continue to

6. All histopathologic studies were made by Dr. Hermann Pinkus, 125 Maple Boulevard, Monroe, Mich.

complete involution. The fifth patient was asymptomatic and exhibited no clinical evidence of activity of the disease after the completion of sixteen weeks of therapy.

In the remaining 4 patients with discoid lupus erythematosus the disease had been present for two or more years. Previous treatment included bismuth by intramuscular injection, cryotherapy, electrodesiccation, gold salts intravenously and local medication. Two of the 4 patients were placed on oral bismuth therapy because weekly injections of bismuth subsalicylate for six and twelve weeks had failed to check the clinical progression of the disease. In 1 patient progression was checked following one week of therapy with bismuth sodium triglycollamate, and the disease was considered clinically inactive after sixteen weeks. This patient was a Negro who presented complete depigmentation of the central portions of the lesions. When treatment was discontinued more than 50 per cent of each lesion had assumed the color of the surrounding skin. In the other case, that of a Negro woman who had discoid lesions of the scalp of eight years' duration, the progression was checked after two weeks of oral bismuth therapy and improvement continued to about 50 per cent involution. At that time there occurred an exacerbation consisting of recurrence of erythema and pain in the lesions. Intermittent periods of remission and exacerbation have continued to the present. The patient is an alcoholic addict, and it is questionable whether treatment was carried out faithfully.

A white woman who has had chronic discoid lupus erythematosus for eighteen years was placed on oral bismuth therapy because of the development of an active lesion of the right cheek after a two year period of inactivity. The patch was raised, bluish red and extremely pruritic. After three weeks of treatment it was flat and pale, and the pruritus had ceased.

The last case in this group is mentioned only because treatment with the drug had to be discontinued. Although the patient did not experience nausea, intestinal cramps or other symptoms he was embarrassed on three occasions by a sudden and forceful evacuation of fluid stools.

Two patients with subacute disseminated lupus erythematosus and 1 patient with the acute disseminated form complete this disease group.

A Negro woman aged 34 had lesions of the face, neck and chest of two months' duration. The individual lesions were of the discoid type with edema, scaling, keratotic follicular plugs and hyperpigmentation of the sharply marginated borders. Central atrophy was not present. A biopsy was performed, and the pathologist's report of histologic sections was compatible with the clinical observations. At the conclusion of six weeks of treatment with the bismuth preparation all signs of activity had disappeared. The skin was soft and pliable, and the only residual change was persistence of the marginal hyperpigmentation.

A Negro woman aged 38 was seen with a maculopapular eruption of the face, neck and chest which had been slowly progressive for three months. The dermatitis

was not easily seen against the dark skin, and the patient sought medical attention chiefly because of a severe pruritus. A diagnosis of lupus erythematosus was made after study of histologic sections. The pruritus had ceased at the end of two weeks of therapy, and there was complete involution of the lesions at the end of one month. There were no residual changes in the skin.

A white man aged 50 was seen on the medical ward acutely ill with lupus erythematosus and an associated polyarthritis. He had had an erythematous dermatitis of the exposed areas of the face, neck and arms following exposure to the sun for the past eight summers. This subsided during the autumn and winter months. Histopathologic studies of sections of the skin exhibited the pathologic features of lupus erythematosus. Examination of the blood revealed that the white blood count was 6,800 and the hemoglobin level was 9 Gm. per hundred cubic centimeters. Urinalysis disclosed no evidence of renal damage. The patient was given sedation, salicylates, crude liver extract, quinine, nicotinic acid, multiple whole blood transfusions and penicillin. During the first four weeks in the hospital he became progressively worse, his temperature ranging from 100 to 103 F., while the cutaneous lesions disseminated to the chest, back, abdomen and extremities. Many bullous and hemorrhagic lesions were present. Treatment of the patient with bismuth sodium triglycollamate was started at the beginning of the fifth hospital week. By the end of the first week of bismuth therapy there was definite improvement in the cutaneous lesions, and by the end of four weeks the lesions were almost cleared and the patient's general condition was good, except for an occasional flare of arthritis. After a total of three months' hospitalization the patient was discharged and followed as an outpatient. The only residual of his dermatitis was a pigmentation in the affected areas. He continued to take two tablets of the drug three times a day after meals for two additional months; then all medication was discontinued. The patient has been observed for two months since the cessation of treatment, and there have been no signs or symptoms of activity of the disease.

LICHEN PLANUS

Eleven patients with lichen planus were treated with the bismuth compound. Eight patients, including 4 white and 1 Negro woman whose ages varied from 23 to 59 years, had generalized lesions. The average duration of the disease was eight weeks, the shortest being two and the longest sixteen weeks. Two white men aged 40 and 54 years had each had generalized lichen planus for six weeks. Biopsies were performed in 2 of the 7 cases, and the diagnosis was confirmed by the histopathologist. All patients in this group had suffered from extremely severe pruritus, which had not been relieved by a variety of local medicaments which had been used previously. Pruritus was appreciably lessened during the first week of oral bismuth therapy in all instances. In all patients except 1 there was complete involution of the dermatitis in from two to eight weeks. It was noted that, in general, the shorter the duration of the disease the shorter was the period of treatment required for cure. Several patients had residual hyperpigmentation following the completion of treatment, but in no instance was there any erythema, papulation or subjective symptoms. One patient failed to

return after her sixth week of bismuth therapy. When last observed she had no subjective symptoms, but a few active lesions were still present.

A white man aged 26 sought medical attention because of annulopapular and serpiginous lesions which had been present on the glans penis for one year. Itching was slight, and no other cutaneous lesions were present. Reaction of the blood to the Kahn test was negative, and the penile lesions had the violaceous color and flat, angular, shining papules which are characteristic of lichen planus. After the patient had three weeks of bismuth therapy, the papular borders had flattened about 75 per cent and had assumed the pinkish color of the surrounding mucosa.

A Negro man aged 43 was seen because of similar lesions which had been present on the left leg for one year. Itching was moderate but sufficient to cause complaint. Reaction of the blood to the Kahn test was negative. All lesions had completely cleared when the patient was observed at the end of twelve weeks of treatment with bismuth sodium triglycollamate.

A case of hypertrophic lichen planus of the left leg was observed in a white man aged 76. The plaque had been present for ten years and covered two thirds of the anterior surface of the leg. The diagnosis was confirmed by histologic study of sections of the lesion. No treatment other than local medication had been given, although the patient had suffered from itching and moderate pain in the hypertrophic plaque when standing or walking. These symptoms were partially allayed after one week of oral bismuth therapy, and the patient was asymptomatic at the conclusion of three weeks of treatment. Although the regimen was continued for twelve additional weeks, only minimal changes could be observed in the hypertrophic plaque.

A white man aged 58 was under observation for one year. The original examination disclosed characteristic flat-topped papules on the flexor surfaces of the wrists. The pathologic diagnosis of tissue sections was lichen planus. During the succeeding six months these lesions persisted and similar ones developed over the sacral region, in the left flank and over the left lower extremity. Pruritus was intense. Treatment was ineffectual and included vitamin B complex parenterally, a preparation containing arsenic trioxide (asiatic pills), eight weekly intramuscular injections of bismuth subsalicylate in doses of 0.13 Gm. each and roentgen therapy to the affected areas. Oral bismuth therapy was then instituted. The pruritus was decidedly ameliorated by the end of the second week, and the involution of the lesions proceeded slowly to completion at the end of twenty weeks of treatment.

SCLERODERMA

Two patients with scleroderma were treated with bismuth sodium triglycollamate. Both were Negro women aged 45 and 43 years, respectively, and both gave a history that covered two years. The face, neck, hands and forearms were involved in both women, and the maximum amount of disability was in the use of the hands. Both patients had painful sensations in the fingers and were able to flex them only one third of the normal degree. One had used several local medicaments, and an antihistaminic preparation had been prescribed but she was unable to continue treatment with it because of severe gastric irritation.

The other had been treated with thyroid, typhoid vaccine, ionization with methacholine chloride and dihydrotachysterol. In neither case was the response to treatment remarkable. After completing five months of therapy 1 patient was able to flex the fingers through two thirds of the normal arc and was relieved of intermittent painful sensations. The other patient was observed while she was taking the drug over a six month period. At the end of that time she stated that she felt much better and was convinced that the treatment had been of value. The skin was more pliable, and the patient was able to flex the fingers about two thirds of the normal degree.

COMMENT

Sodium bismuth triglycollamate appears to be a satisfactory drug for the treatment of those dermatoses which in the past have been found to respond to other forms of bismuth therapy. Further, in some instances oral use of this bismuth preparation produced satisfactory results although previous treatment with bismuth by the intramuscular route had failed. It is likely that further experience will show that the reverse is also true; namely, that occasionally a patient who does not respond to bismuth given orally will do well under treatment with intramuscular bismuth salts.

Toxic manifestations played a minor role. In a few instances gingivitis due to bismuth was noted. In none did it become necessary to discontinue treatment. Development of the gingivitis at times was taken as an indication that the metal was being adequately absorbed.

One patient had a gastrointestinal reaction which was manifested by acute diarrhea of sufficient severity to cause him to discontinue treatment. Reduction of dosage did not prevent the reaction, and further treatment was impossible. No untoward cutaneous reactions were observed.

Of the various types of verrucae treated, the best results by far were obtained against verruca plana juvenilis. Results obtained in the treatment of verruca vulgaris were approximately the same as are usually accomplished when a bismuth salt is used parenterally. It is reasonable to assume that there is less probability that suggestion may play a part when the drug is given by mouth than when it is injected; hence, the foregoing results are presumably due to the pharmacologic action of the metal.

Bismuth sodium triglycollamate was more effective against disseminated lupus erythematosus than against the chronic discoid type. In the latter, however, the response compared favorably with that obtained by other methods of treatment. The drug also proved efficacious as an agent in the treatment of lichen planus; eight weeks, which was the average time required for involution of all lesions, is in our

experience equal to or less than the time required when bismuth is given parenterally.

SUMMARY

1. Forty-six patients whose diseases represented five dermatologic entities were treated with sodium bismuth triglycollamate (bistrimate®).

2. The dose for adults was one tablet (the equivalent of 75 mg. of metallic bismuth in the form of sodium bismuth triglycollamate) three times a day after meals. This dose was doubled after three days if signs of intolerance were not manifest.

3. The dose for children was estimated according to age and weight.

4. Eighteen patients with various types of verrucae were treated with the drug. In 5 of 6 cases, juvenile flat warts were completely cleared after two to four weeks. One patient was unimproved after three weeks of treatment. Four patients with verruca vulgaris were free of lesions after an average of eight weeks of treatment; 5 were improved 50 per cent or more after three weeks of treatment, and 2 were unchanged after three weeks of treatment. One patient with eleven verrucae plantaris was free of lesions after six weeks of treatment. No recurrence was observed during a two month period.

5. Three patients with condyloma acuminatum attained approximately 90 per cent involution of the lesions after seven, sixteen and twenty weeks of treatment.

6. Twelve patients with lupus erythematosus were observed while on oral bismuth therapy. Nine of them had lesions of the chronic discoid type. Five of them manifested great improvement in both symptoms and clinical appearance, but lesions were not completely inactive after three to twelve weeks of treatment. Two patients with discoid lesions exhibited no clinical signs of activity after sixteen weeks of treatment, while 1 did not improve after an equal period of therapy. One patient discontinued treatment after one week because of intolerance to the drug. Two patients with subacute disseminated lupus erythematosus were clinically inactive after four to six weeks of therapy. One patient with acute disseminated lupus erythematosus had a downward course under various types of treatment. Clinical improvement took place after oral bismuth therapy was started, and clinical recovery was achieved after six weeks of treatment.

7. Eleven patients with lichen planus received the drug. In 7 of 8 patients generalized lesions showed complete involution after two to eight weeks of treatment. One patient was improving satisfactorily but failed to return for observation after the sixth week. Pruritus was relieved early in the course of treatment in all instances. Two patients with annulopapular lesions of the glans penis and of the left leg, respec-

tively, responded satisfactorily to treatment. The former showed 75 per cent improvement during the three weeks that he was under observation; the latter had complete involution of the lesions at the end of twelve weeks. One patient with hypertrophic lichen planus manifested only minimal improvement in the plaque at the conclusion of twelve weeks of treatment, but the patient was asymptomatic at the end of three weeks.

8. Two patients with scleroderma obtained moderate clinical improvement while under treatment with bismuth sodium triglycollamate.

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A SEVERE FORM OF ACNE DEVELOPING IN THE TROPICS

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ACNE usually is not considered a disabling disease. In the recent war it was found, however, that such was not the case in the tropics. In this area a severe form of acne developed which was characterized by large pustules, draining sinuses and extensive, disfiguring scars, frequently keloidal. This condition became known among the medical officers as "tropical acne." Because of its severity and the disability it incurred, this form of acne merits further discussion.

The importance of this disease is shown in the report of Cohen and Pfaff,[1] who stated that acne vulgaris was the most serious problem in the tropics. Other dermatologists with whom they came in contact were in agreement that patients having this disease were permanently unfit for tropical duty. Kley,[2] writing on cutaneous disease aboard ship, noted that acne vulgaris was second in occurrence, fungous infections being the first. McLaughlin,[3] discussing tropical skin diseases, commented on the severity of acne in his experience. Sulzberger and associates,[4] studying the dermatologic patients on the island of Guam, found an incidence of 20 per cent of tropical acne.

Duemling [5] found that acne was a close second to fungous infections among naval patients being evacuated from the tropics because of cutaneous diseases. A similar report which I made [6] showed that tropical acne accounted for 28.5 per cent of all patients with dermatologic diseases arriving from overseas who were seen in the four months from July through October 1945 in the United States Naval Receiving Hospital, San

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Read at the Sixty-Seventh Annual Meeting of the American Dermatological Association, Inc., Murray Bay, Quebec, Canada, June 2, 1947.

1. Cohen, T. M., and Pfaff, R. O.: Penicillin in Dermatologic Therapy, Arch. Dermat. & Syph. **51**:172-177 (March) 1945.

2. Kley, E. C.: Skin Disease Aboard a Destroyer, U. S. Nav. M. Bull. **41**:407-408 (Feb.) 1944.

3. McLaughlin, R. R. M.: Treatment of Tropical Skin Diseases in the South Pacific, U. S. Nav. M. Bull. **45**:314-322 (Aug.) 1945.

4. (*a*) Sulzberger, M. B.; Addenbrook, E. G.; Joyce, S. J.; Greenberg, S., and Mack, A. G.: Tropical Acne, U. S. Nav. M. Bull. **46**:1178-1184 (Aug.) 1946; (*b*) Tropical Acne, Bull. U. S. Army M. Dept. **6**:149-154 (Aug.) 1946.

5. Duemling, W. W.: Cutaneous Disease in South Pacific, Arch. Dermat. & Syph. **52**:75-86 (Aug.) 1945.

6. Novy, F. G., Jr.: Tropical Acne, California Med. **65**:274-277 (Dec.) 1946.

Francisco. During the same period fungous infections, which headed the list, had an incidence of 29.4 per cent of the total.

In the Army, the incidence of acne among those evacuated because of cutaneous disease was not as high as in the Navy. This fact can be explained by Nisbet's observation [7] that over 80 per cent of the Army dermatologic evacuees had quinacrine hydrochloride (atabrine dihydrochloride®) dermatitis. In the Navy this type of dermatitis never accounted for more than 10 per cent of the cases of cutaneous disease.

Severe acne in the tropics was known before the war but did not receive much attention. Castellani and Chalmers,[8] in their text on tropical diseases, stated that acne is common to all races and mentioned acne indurata and acne papulosa. Fasal,[9] in a personal communication, wrote that severe acne was a problem among the white persons coming to Malaya, particularly in the males, although occurring in both sexes. He stated the belief that the extreme heat, and not changes in living conditions or diet, is a predisposing factor for the development of this condition.

This disease differs in many respects from the adolescent type of acne vulgaris. It is, nevertheless, a definite form of acne in that comedos, inflammatory nodules, cysts and pustules associated with the sebaceous glands are present. Furunculosis, impetigo and pyoderma are frequent complications of this condition, but the lesions of acne are the primary ones.

The following characteristics of tropical acne will show how this disease differs from the forms of acne associated with the temperate climates.

AGE OF PATIENTS

It was found that patients with this disease were considerably older than those with adolescent acne. The average age of 51 patients studied by Sulzberger [4] was 22.0 years. The range of age was from 16 to 37. Twenty-five of the patients were over 20 years of age when their acne began. In my series of 100 patients [6] the average age was 22.75 years. Eleven persons were over 30 years of age. One of these was 41 years old. Of this older group, all gave the history of not having been bothered with acne for years. Hinrichsen and Ivy [10] gave the average age of severe involvement for boys in the Chicago area as between 16 and 19 years. Many of the enlisted personnel in the tropics were

7. Nisbet, T. W.: A New Cutaneous Syndrome Occurring in New Guinea and Adjacent Islands, Arch. Dermat. & Syph. **52**:221-226 (Oct.) 1945.

8. Castellani, A., and Chalmers, A. J.: Manual of Tropical Medicine, ed. 3, New York, William Wood & Company, 1919.

9. Fasal, P.: Personal communication to the author.

10. Hinrichsen, J., and Ivy, A. C.: Incidence in the Chicago Region of Acne Vulgaris, Arch. Dermat. & Syph. **37**:975-982 (June) 1938.

in this same age group, but this group was not the one in which tropical acne was found.

RELATION TO PREVIOUS ACNE

In the published accounts of two series of cases of tropical acne,[11] considerable variation in the relation to previous acne was found. In Sulzberger's cases 24 patients had no history of signs of acne, while 27 had evidence of previous acne. In the cases that I reported 98 of 100 patients gave a history of previous acne. The difference might be explained by the fact that many in the latter series at first denied having had acne until they were asked whether they had had "blackheads or pimples." The present disease was so much more severe and disfiguring than their previous acne that it did not seem to them that the two conditions could be related. Most of these patients had had a very mild acne consisting of comedos and a few pustules. The patients' average age at onset of the previous acne was 15.8 years. The face was involved in 82 patients, the neck in 6, the back in 6 and the chest for 2. As was stated before, 2 patients gave no history of previous acne. Sulzberger, in discussing this point, suggested that many persons denied having previous acne because they wanted to have their cutaneous trouble attributed to military service. In neither series was there a high incidence of severe previous acne; Sulzberger had only 2 patients who had had it. It is evident from the foregoing data that severe acne vulgaris is not a precursor of tropical acne.

INCUBATION PERIOD

Nine patients stated that they had had activity of their acne before going overseas. Fifty-two began having trouble within six months after arriving in the tropics. The fact that the eruption started so quickly after they had reached the hot climates would seem to rule out the possibility of any dietary factor or the effect of chronic fatigue from military duties in causing the eruption. This form of acne was not associated with cachexia, so that it is not a form of acne cachecticorum.

SITES OF INVOLVEMENT OF TROPICAL ACNE

As is noted in the table, in a total of 151 cases the back was involved in 126 patients; and the chest next most frequently, in 87 patients, and the neck in 73 persons. Activity involving the face occurred in only 42 patients. This observation is in contrast to that concerning the previous acne, in which 82 per cent of the patients had involvement of the face. The statistics also show a high incidence of involvement of the thighs and the buttocks. In Sulzberger's series this was 31.36 per cent, as contrasted with findings on the juvenile type of acne vulgaris, in which involvement

11. Sulzberger et al.[4] Novy.[6]

in this location is extremely rare. The distribution was similar to that described by Michelson and Allen [12] for acne conglobata.

No cases were observed in which the eruption extended into the scalp and thus suggested dissecting cellulitis of the scalp (perifolliculitis capitis abscedens et suffodiens), a condition which, according to Barney's statement,[13] has a close relationship to acne conglobata.

In relation to this difference of the sites of activity in juvenile acne and tropical acne, it was frequently noted that the sites of the old acne were not exacerbated and often were clear, while new areas showed extensive involvement. For example, a patient might have scarring and a few comedos on his face due to his previous acne, while his shoulders and back would be covered with deep cystic, pustular and granulomatous lesions due to tropical acne of recent development. This observation suggests that sites previously involved by adolescent acne may be resistant to tropical acne.

Sites of Involvement of Tropical Acne

Author	Sulzberger and Associates[4]	Novy	Total
No. of cases	51	100	151
Sites			
Back	42	84	126
Chest and/or abdomen	35	52	87
Neck, posterior, anterior and/or lateral	24	49	73
Arms and/or forearms	25	18	43
Face	14	28	42
Buttocks and thighs	16	14	30

DESCRIPTION OF THE LESIONS

In observing patients with tropical acne one is immediately struck by the severity of the disease. While deep-seated cystic acne is occasionally seen among groups of patients with acne vulgaris in temperate climates, this type of eruption is the rule among those with tropical acne. It has many features in common with acne conglobata; however, tropical acne is an acute disease, while acne conglobata is a chronic one.

Numerous large comedos were found in the involved areas. In many patients comedos were present over the entire back, buttocks, thighs and arms. Groups of comedos, as described for acne conglobata, were also seen. Double comedos were noted on many occasions.

The ordinary papules of acne were not often observed because the lesions of tropical acne were larger and are better described as nodules.

12. Michelson, H. E., and Allen, P. K.: Acne Conglobata, Arch. Dermat. & Syph. **52**:49-67 (Jan.) 1931.

13. Barney, R. E.: Dissecting Cellulitis of the Scalp (Perifolliculitis Capitis Abscedens et Suffodiens), Arch. Dermat. & Syph. **23**:503-519 (March) 1931.

They became very painful when secondarily infected. In many patients the entire upper portion of the back and chest was studded with these lesions, large plaques being formed. The lesions would first appear associated with a comedo as simple sebaceous retention cysts, with no change in the overlying skin. They rapidly became larger and secondarily infected. This infection would produce softening, redness and pain, and then the nodules would rupture, discharging a thick white or greenish pus and blood. When the exudate dried there was extensive crusting. On removal of this crusted portion an ulcer with bright red granulation tissue was found. When the disease was severe the individual nodules would be so close together that they would form plaques. These plaques had many draining sinuses, with subcutaneous communications between them. Pressure on one point would cause a discharge of pus several centimeters away. These lesions were so painful that the wearing of bandages and dressings was extremely uncomfortable. Many patients found that it was impossible to carry on their military duties.

Many of the lesions were linear. Some of them were 8 to 10 cm. long and 2 to 3 cm. wide. Fistulous openings would appear in several places along these cysts. These tubular lesions were probably due to several lesions' becoming confluent. They were seen particularly about the neck and lower part of the face. These lesions were similar to those described by O'Leary and Kierland,[14] under the title of pyoderma faciale.

After the nodules opened they might drain for many weeks. As the drainage became chronic, the exudate became yellowish, with an oily, gelatinous consistency. At times there would be an increase in drainage, due to the subcutaneous channeling through of purulent material from a neighboring lesion. As the discharge lessened, healing would begin to take place, with the area filling in with granulation tissue, after which there was scar formation. Many of these scars were hypertrophic, and definite keloids were formed. The incidence of keloid formation was very high. About the face and neck many patients had long linear keloids and were badly disfigured in much the same way as are women who have had pyoderma faciale.

On the chest and shoulders extensive hypertrophic scarring was noted. In some of the patients there were hand-sized areas of scarring. In some instances these large areas would have bridges of normal tissue with comedos like those described as characteristic of acne conglobata.

RACE

The American Negro appears to be particularly free from this disease. Several dermatologists who have seen large numbers of these cases do

14. O'Leary, P. A., and Kierland, R. R.: Pyoderma Faciale, Arch. Dermat. & Syph. **41**:451-462 (March) 1940.

not recall having seen a single case in a Negro.[15] My own experience has been similar. Livingood,[16] on the other hand, wrote that he had seen a few cases in the Negro troops in the India-Burma theater. This observation is somewhat surprising in view of the fact that Hinrichsen and Ivy[10] in Chicago found a slightly higher incidence of severe acne vulgaris among Negroes than among white persons. Hazen[17] also found that acne was a common disease of the Negroes. In his series of 11,729 Negroes with cutaneous disease, 1,140 had acne vulgaris.

Castellani and Chalmers,[8] in their text on tropical diseases, stated that acne is a common disease among the natives of tropical countries. Fasal[9] also noted many natives with acne vulgaris but not one with this severe type of involvement. Wolfe[18] recently examined 1,047 natives in New Guinea for diseases of the skin. He found that 57 per cent were normal. Among the group having cutaneous diseases acne was seventh on the list, with an incidence of 0.6 per cent. He did not go into the details as to the type or the extent of their acne. Among the natives around the camps or in the hospitals of the Southwest Pacific the author never saw any form of acne suggestive of this type. It would seem, therefore, that the dark-skinned races are free of this disease and that it is a disease of white persons in the tropics.

SEX

Tropical acne is not limited to the male sex, as a few cases have occurred among nurses and other women in the services.[19] These cases have been typical and severe.

ETIOLOGIC CONSIDERATIONS

The etiology of tropical acne, as of adolescent acne, is unknown. For one to have a clearer understanding of why this disease develops in certain persons, many factors should be considered. For convenience in discussion they will be placed under separate headings.

Psychogenic Factors.—It is very difficult for one to evaluate the emotional and psychologic upsets that go along with war and their effect

15. (*a*) Bagby, J. W.: Personal communication to the author. (*b*) Pfaff, Richard, O.: Personal communication to the author. (*c*) Duemling, W. W.: Personal communication to the author. (*d*) Nisbet, T. M.: Personal communication to the author.

16. Livingood, C. S.: Personal communication to the author.

17. Hazen, H. H.: Syphilis and Skin Diseases in the American Negro, Arch. Dermat. & Syph. **31**:316-323 (March) 1935.

18. Wolfe, W. D.: Diseases of the Skin Among the Natives of Northeast New Guinea, Arch. Dermat. & Syph. **52**:247-249 (Oct.) 1945.

19. (*a*) Bagby, J.: Personal communication to the author. (*b*) Duemling, W. W.: Personal communication to the author. (*c*) Livingood, C. S.: Personal communication to the author.

on the development of acne. It is well known that emotional upsets and stress and strains will exacerbate acne vulgaris. This has been discussed at length by Stokes and Sternberg.[20] The patients with tropical acne, however, did not fall into the group of the emotionally unstable. During the war I had the opportunity to observe large numbers of neuropsychiatric patients, and tropical acne was only occasionally seen among them.

Living Conditions.—In the combat areas living conditions naturally were very poor, with inadequate bathing and laundry facilities. The diet, likewise, was of the "canned" variety, with no fresh vegetables or meat. In the Navy, however, the great majority of patients did not have these unfavorable living conditions. Most of them were stationed either at well established bases or aboard ship. In both of these locations there were good bathing accommodations and laundries. The diet, likewise, was well balanced, and fresh vegetables and fresh meat were frequently available. It does not appear that diet, infrequent bathing and dirty living conditions could account for tropical acne. The onset of this disease occurred in the first few months overseas. If tropical acne occurred on a basis of poor diet and filth many new cases would develop and would continue to develop after persons had had many months of exposure to unhealthy conditions, but they did not.

Type of Duty.—It is generally true that dirty and greasy occupations are predisposing causes of acne. My group of 100 patients were questioned as to the type of duty they had performed. Forty-two had had duty aboard ship, and 58 had had duty ashore. Of the group aboard ship 37 had had duty above deck, which, for the most part, is considered clean duty. In addition, there were others who had been working as radio operators, in small boat crews, etc., in occupations which are primarily not considered dirty work. There were only 2 machinists and 1 cook in the entire group.

Of the 58 persons based ashore 21 had dirty, oily jobs; these men were motor drivers, machinists and stevedores. The others had clean duty, working as guards, mailmen, pharmacists' mates and communicators. Thus, it appears obvious that duties in themselves were not a primary factor in the development of tropical acne.

Effect of Clothing and Tanning.—It has been shown that tropical acne occurs for the most part on the normally covered parts, namely, the back and the chest. During the war there was considerable discussion among the medical officers as to what part clothing played in precipitating acne in the tropics. Some felt that going without shirts and having excessive exposure to sunlight predisposed persons to the development

20. Stokes, J. H., and Sternberg, T. H.: A Factor Analysis of the Acne Complex with Therapeutic Comment, Arch. Dermat. & Syph. **40**:345-368 (Sept.) 1939.

of this disease. Others thought that the wearing of shirts in the tropics was detrimental because it did not allow tanning, which might help to control the disease. They also felt that the rubbing of the shirts on the perspiring skin caused irritation and resulted in the formation of pustules.

For these reasons 36 patients were questioned about the wearing of shirts. It was found that 21, or 59 per cent, did not wear them most of the time and that 15, or 41 per cent, did. This ratio was roughly the same as that seen among the naval personnel. It appeared, therefore, that the wearing or not wearing of shirts did not have any relationship to the development of tropical acne. Tanning of the skin did not prevent the disease, as many patients who had a deep coat of tan were observed. In some cases, however, as in patients with prickly heat, there seemed to be some improvement after a good coat of tan had been obtained.

Blood Chlorides.—It has been stated that increasing the chloride intake was beneficial in cases of acne vulgaris.[21] Reasoning conversely, it was thought that this severe form of acne might be due in part to the lowering of blood chlorides, which would be expected with profuse sweating. Determination of blood chlorides was done on 50 consecutive patients with tropical acne the morning following their arrival in the United States. As controls 50 neuropsychiatric patients with clear skins were used. The latter were chosen as nearly as possible from the same incoming draft, so that they had experienced the same climatic conditions. Their blood also was drawn the first morning after their arrival. The two groups both showed normal blood chlorides; and the average for the patients with acne was 460.52 mg. and that of the controls 468.53 mg. per hundred cubic centimeters. This observation means that there was no definite inbalance of blood chlorides among these patients at the time the examinations were made. Different results might have been obtained if the tests had been made in the tropics at the time the acne first developed.

Effect of Climate.—The hot, humid climate of the tropics appears to be the most important cause of this disease. The heat produces an overactivity of the sebaceous glands, which results in plugging of the ducts and leads to comedos and cyst formation. Secondary infection takes place, producing pustules and pyoderma. This result, in turn, produces the ulceration and granulomas, which development causes scarring on involution. There must also be an individual predisposition to acne to explain why this disease develops only in certain persons. The histories in my series bear this theory out, as 98 of the patients did have some acne in their younger years. In most instances this was of a mild form. The history of severe adolescent acne was rare.

21. Wise, F., and Sulzberger, M. B.: The Year Book of Dermatology and Syphilology, 1932-1937, Chicago, The Year Book Publishers, Inc., 1933, p. 11.

That extreme heat and high humidity are sufficient in themselves to produce this kind of acne in a person with seborrheic or acne diathesis is further suggested by the recent observations on prickly heat and thermogenic anhidrosis. In histologic studies on patients with prickly heat Sulzberger and Zimmerman [22] have confirmed the earlier work of Pollitzer in showing that the orifices of sweat glands are plugged with plaques of squamous epithelial cells. Behind this is found a distention of the ducts, with a cellular, inflammatory response in the cutis. These changes are explained on the basis that continual sweating causes maceration of the surface of the skin and faulty keratinization, resulting in filling of the sweat gland orifices with cellular debris.

Similar histologic changes were found in a patient with thermogenic anhidrosis.[23] The sweat glands were filled with keratin plugs. The ducts themselves were distended and ruptured, with fluid extravasated into the surrounding tissue. The explanation was also on the basis of excessive sweating and maceration of the outer layers of the epidermis, resulting in closing off of the duct orifices with cellular elements.

From these investigations it seems reasonable to assume that the same process happens to the sebaceous glands. They are subject to the same macerating effect of the skin, and the epithelial cells could plug the orifices of the glands, causing comedo formation. Later the nodules could become infected to produce pustules and pyodermic lesions.

HISTOLOGIC OBSERVATIONS

Three biopsy specimens were obtained from a patient with typical tropical acne soon after he had returned to this country. These were of a comedo, an early inflammatory cyst and a late cystic lesion.

The comedo showed on microscopic examination an appreciably dilated sebaceous gland filled with sebaceous and keratinized material. Surrounding this gland was a very slight infiltrate of lymphocytes. The blood vessels of the corium were somewhat enlarged and also had a slight lymphocytic infiltrate. The epidermis appeared normal.

In the early cyst there was found a very much enlarged sebaceous gland, with abscess formation. In the center was a large plug made up of sebaceous and keratin material. Surrounding this was an exudate of polymorphonuclear leukocytes and lymphocytes. Around the sebaceous gland was a wide band of inflammatory infiltrate, which in places extended to the adipose tissue. This infiltrate was primarily

22. Sulzberger, M. B., and Zimmerman, H. M.: Studies on Prickly Heat: II. Experimental and Histologic Findings, J. Invest. Dermat. **7**:61-68 (Feb.) 1946.

23. Sulzberger, M. B.; Zimmerman, H. M., and Emerson, K., Jr.: Tropical Anidrotic Asthenia (Thermogenic Anhidrosis) and Its Relationship to Prickly Heat, J. Invest. Dermat. **7**:153-164 (Aug.) 1946.

made up of leukocytes. No giant cells were noted. The blood vessels were dilated and had a perivascular infiltrate of lymphocytes. The epidermis was somewhat thickened, and there was a flattening out of the rete pegs.

Biopsy of the late lesion revealed a more advanced state of inflammatory reaction. The sebaceous gland was nearly destroyed by the abscess formation. Throughout the corium was a scattered dense infiltrate. This was particularly noted about the blood vessels. In the deeper layers of the corium there were some fibroblastic proliferation and many lipid histiocytes. Multinucleated giant cells were also found in this area. The epidermis showed acanthosis, with thickening and hypertrophy of the rete pegs.

The findings in this case were similar to those in cases of severe acne vulgaris.

PROGNOSIS AND TREATMENT

While they remained in the tropics the condition of these patients usually became progressively worse. More and more lesions developed, and the areas of involvement became more extensive. This development led to complete disability, so that large numbers had to be returned to cooler climates. The usual treatment for acne vulgaris was not effective in the tropics.

On arrival in this country many of the patients began to notice improvement in a short time, without any definite therapy. In mild cases there was great improvement in a cooler climate as a result of such simple measures as daily baths and the use of a paste containing 2 per cent resorcinol and 10 per cent precipitated sulfur.[24] Duemling [5] reported good results after exteriorization of the cysts and pustules. This was done by removal of the overlying skin and packing with iodoform gauze, allowing the base to heal over. This procedure produced smooth, flat scars instead of the thick, hypertrophic type. The severer scars usually resulted from incision and drainage or occurred when deep lesions were allowed to involute slowly by themselves. With these methods and roentgen therapy many patients had clearing of the skin except for the residual scarring. Some persons, however, have continued to acquire new lesions after having been out of the tropics for over two years. Of course, those who were unfortunate enough to have keloids develop are still seeking medical aid.

SUMMARY

The clinical features of tropical acne have been described. It differs from acne vulgaris in the following ways: 1. It occurs in an older age group. 2. Its development is more rapid. 3. It occurs most

24. Duemling, W. W., in discussion on Novy.[6]

frequently on the back and chest, whereas the usual acne vulgaris involves the face. 4. The lesions are more destructive, leaving severe, mutilating scars. 5. The colored races are apparently immune.

Tropical acne clinically resembles acne conglobata very closely. They both occur in an older age group. The sites of involvement, namely, the back and chest, are similar. The buttocks and the thighs are commonly affected in each disease. The type of eruption is also similar in the two diseases. Both show a widespread distribution of large comedos. The tendency to form plaques with numerous fistulous openings and subcutaneous communications between lesions is characteristic of both diseases. The two diseases differ from one another in that acne conglobata is a chronic disease lasting for years while tropical acne develops in a few months after the person's exposure to the tropical climate. Tropical acne, in the majority of cases, tends to heal on the patient's return to cooler climates. This climatic response to the evolution and involution of tropical acne would suggest that this disease is not a variant of acne conglobata.

Psychogenic factors, living conditions, type of duty and clothing are not important in the development of this disease of the skin.

This form of acne is apparently due to stimulation of sebaceous glands by excessive heat and moisture in persons who have seborrheic or an acneform condition of skin.

With present knowledge it is impossible for one to predict who is likely to acquire tropical acne on going to hot climates.

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NATURE OF ANTIGENS AND ANTIBODIES IN SEROLOGY OF SYPHILIS

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SEROLOGIC tests for syphilis have come to be recognized as necessary laboratory aids in the diagnosis, management and prognosis of clinical syphilis. Yet, for many years the actual antigen-antibody mechanisms involved have not been adequately explained. The apparent anomaly of lipidal beef heart antigen's being associated with a high degree of specificity in reacting with syphilitic serum has been a source of much concern, especially to the immunologist. It is not the purpose of this report to solve this vexing problem, but to review the present immunologic and physicochemical concepts of the nature of the antigens and antibodies involved.

ANTIGENS

The nature of the antigens involved in the serologic tests for syphilis will be considered first. In the original serologic test for syphilis, Wassermann, Neisser and Bruck [1] discovered that aqueous extracts of syphilitic tissue effected complement fixation when mixed with syphilitic serum. One year later, Laridsteiner and his co-workers [2] successfully employed alcoholic extracts of normal mammalian tissue in the same test. This served to discredit the theory that the Wassermann reaction was a specific one, i. e., that the reactive substance in syphilitic serum was an antibody specific to Treponema pallidum.

Many theories have been advanced to account for this apparently nonspecific reaction in syphilis. These include such vague concepts

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1. Wassermann, A.; Neisser, A., and Bruck, C.: Eine serodiagnostische Reaktion bei Syphilis, Deutsche med. Wchnschr. **32**:745, 1906.

2. Landsteiner, K.; Müller, R., and Pötzl, O.: Zur Frage der Komplementbindungsreaktionen bei Syphilis, Wien. klin. Wchnschr. **20**:1565, 1907.

as abnormal labilization of the serum globulin. Pierce and Breazeale [3] showed that lipidal antigens acted as zeolites (hydrated double silicates) in effecting a change of base. When either of these antigens was added to syphilitic serum, the calcium content of the latter was reduced. This observation would tend to give credence to the theory that the antibody is a divalent cation, like calcium, or magnesium, or both.

The concept of the nonspecific nature of the serologic reaction for syphilis remained unchallenged for many years, prior to the employment of the spirochetal antigens. In 1940 Erickson and Eagle [4] investigated the serologic antigenicity of "palligen," a phenolized suspension of the Reiter strain of spirochete, approximately 10^9 organisms per cubic centimeter, in a series of 490 syphilitic serums. In this study they obtained a higher degree of sensitivity and specificity with the spirochetal antigens than with the routine Wassermann and Eagle lipidal antigens. This evidence would point toward the specific nature of the reactive substance. Eagle and Hogan [5] hypothesized that T. pallidum, as well as the cultured spirochetes, contains an antigenic factor (lipidal) which resembles the reactive constituent (lipidal) of tissue extract. This concept was confirmed by Beck,[6] who demonstrated that cultured spirochetes contain a substance extracted by alcohol which qualitatively resembles tissue lipids in its reactivity with syphilitic serum.

Kolmer and his co-workers,[7] employing a similar spirochetal antigen ("palligen"), in tests with serums of patients with syphilis, malaria and leprosy, observed a higher incidence of false positive reactions in the latter two diseases with the spirochetal antigen than with the routine lipidal antigens. This situation they attributed to the presence, in normal and in nonsyphilitic serums, of naturally occurring antibodies for nonpathogenic spirochetes which are capable of fixing complement with antigens of alleged T. pallidum.

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3. Pierce, L. F., and Breazeale, F. L.: Removal of Divalent Cations from Solution by Beef Heart Antigens, J. Invest. Dermat. **5**:249 (Oct.) 1942.

4. Erickson, P. T., and Eagle, H.: Evaluation of Spirochete Complement Fixation Reaction in Comparison with the Eagle Flocculation and Wassermann Procedures, Ven. Dis Inform. **21**:31 (Feb.) 1940.

5. Eagle, H., and Hogan, R. B.: On the Presence in Syphilitic Serum of Antibodies to Spirochetes, Their Relation to So-Called Wassermann Reagin, and Their Significance for the Serodiagnosis of Syphilis, J. Exper. Med. **71**:215 (Feb.) 1940.

6. Beck, A.: Rôle of Spirochaete in Wassermann Reaction, J. Hyg. **39**:298 (May) 1939.

7. Kolmer, J. A.; Kast, C. C., and Lynch, E. K.: Studies on the Rôle of Spirochaeta Pallida in the Wassermann Reaction: Complement Fixation in Syphilis, Leprosy and Malaria with Spirochetal Antigens, Am. J. Syph., Gonor. & Ven. Dis. **25**:300 (May) 1941.

The employment of spirochetal antigens to this date has been fraught with many discrepancies, and the frequency of false positive reactions has rendered them inferior in specificity to the lipidal antigens. The organisms utilized for these antigens were avirulent, and much doubt exists as to their relation to the spirochete of syphilis. The general belief is that they were saprophytic nonvirulent spirochetes contaminating the lesions from which T. pallidum was supposedly obtained.

The cultivation of a truly virulent T. pallidum in vitro offers the greatest hope for understanding the true nature of antigen-antibody reactions in syphilis. This antigen would be expected to give the most specific and sensitive results in serologic tests for syphilis. Nelson,[8] at the Johns Hopkins University, recently succeeded in maintaining the life of the Nichols strain of T. pallidum on artificial mediums. This organism has been shown to be virulent for human beings as a result of accidental inoculation of a laboratory worker. Using a special basal medium, Nelson has been able to maintain the life of the treponemes for fourteen days, with a "half-life" period of from six to eight days. Unfortunately, as yet, the quantity of spirochetes thus obtainable is numerically insufficient to permit the general use of these organisms as an antigen in serologic tests for syphilis. Yet they have been employed to demonstrate the existence of a specific antibody in syphilitic serum.

Until the time that such specific antigens can be made available for routine use in serologic tests for syphilis, it is necessary to depend on the recognized lipidal antigens. In considering the chemical nature of these antigens, Eagle[9] and others expressed the opinion that the reactive substance in tissue extracts is a phosphatide. Immunologically, it may fall into the group of haptens which can combine with a specific antibody but which cannot itself induce the formation of such an antibody unless combined with a Schlepper antigen.

In recent years a more purified antigen substance has been isolated from the lipids of beef heart. Pangborn[10] separated from crude lipid mixtures the substance cardiolipin, a phosphatide which when properly combined with mixtures of lecithin and cholesterol serves as a uniform

8. Nelson, R. A., Jr.: Factors Affecting the Survival of T. Pallidum in Vitro, Am. J. Hyg. **48**:120 (July) 1948.

9. Eagle, H.: The Laboratory Diagnosis of Syphilis: The Theory, Technic, and Clinical Interpretation of the Wassermann and Flocculation Tests with Serum and Spinal Fluid, St. Louis, C. V. Mosby Company, 1937, p. 49.

10. Pangborn, M. C.: A New Serologically Active Phospholipid from Beef Heart, Proc. Soc. Exper. Biol. & Med. **48**:484 (Nov.) 1941.

standard antigen. In addition, such antigens have been shown to give fewer nonspecific serologic reactions than the cruder lipidal mixtures. This fact was clearly demonstrated by Rein and Kent [11] and others in regard to false positive serologic reactions in malaria.

ANTIBODIES

On the basis of experiments with "palligen," Eagle and Hogan [5] demonstrated the presence of two antibodies in syphilitic serum: an antilipidal antibody and an antitreponemal antibody. When syphilitic serum was adsorbed with an excess of beef heart lipidal antigen, all reagin antibody was removed. The reagin-free filtrate still gave agglutination and complement fixation reactions with spirochetal suspensions in the same titer as in the original serum. However, when the same serum was adsorbed with spirochetal suspensions, its reactivity with both lipidal and spirochetal antigen was removed.

Recent studies by a group of other investigators confirmed the presence of multiple antibodies in syphilitic serum. D'Alessandro,[12] in working with "palligen," demonstrated the presence of three distinct antibodies in syphilitic serum: antilipidal, antitreponemal (thermolabile) and antitreponemal (thermostable). He expressed the belief that in early primary syphilis the antitreponemal antibodies manifest themselves before the antilipidal antibodies. In secondary and tertiary syphilis both types run a parallel course. In cases of prenatal syphilis the antilipidal antibody often exists alone.

The work of d'Alessandro was confirmed by Puccinelli and Oddo,[13] who described the technic of demonstrating the three antibodies.

The most convincing evidence to date of the existence of a specific antitreponemal antibody in syphilitic serum stems from the work of Nelson and Mayer.[14] These workers demonstrated the presence of immobilizing antitreponemal antibodies. Employing the virulent Nichols strain of T. pallidum, kept alive on a special basal medium, they showed that these actively motile spirochetes lost their motility when incubated

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11. Rein, C. R., and Kent, J. F.: False Positive Tests for Syphilis: A Study of Their Incidence in Sporozoite-Induced Vivax Malaria, J. A. M. A. **133**:1001 (April 5) 1947.

12. d'Alessandro, G.: The Nature of the Wassermann Reaction and the New Serology of Syphilis, Boll. d. Ist. sieroterap. milanese **25**:138, 1946.

13. Puccinelli, V. A., and Oddo, F.: Contribution to the Study of Syphilitic Serum, Gior. ital. dermat. e sif. **87**:447 (Dec.) 1946.

14. Nelson, R. A., and Mayer, M. M.: Immobilization of T. Pallidum in Vitro by Antibody Produced in Syphilitic Infection, J. Exper. Med. **89**: 369 (April) 1949.

at 35 C. for sixteen hours in the presence of syphilitic serum. No such immobilizing effect was observed with normal and with false positive control serum. In addition, these workers demonstrated that this immobilizing antibody was distinct and separate from the antilipidal antibody. On the adsorption of all the reagin of syphilitic serum with lipidal antigens until the filtrate gave negative flocculation and complement fixation reactions, the immobilizing effect of the serum remained unaltered. The same specific immobilizing antibody has been demonstrated by these workers in the spinal fluids of patients with untreated syphilis of the central nervous system.

Because a truly virulent T. pallidum was employed in this work, these workers have made a distinct contribution to the immunology of syphilis by demonstrating what appears to be a truly specific antitreponemal antibody.

Comparative Titers in Mother and in Fetus (Kahn Units)

	Mother	Fetus
Flocculation Tests		
Kahn standard	16	2
Mazzini	30	9
Venereal Disease Research Laboratory cardiolipin	6	—
Kline exclusion	48	4
Rein-Bossak cardiolipin	31	2
Complement Fixation Tests		
Kolmer	14	14
Cardiolipin	36	36

The work of Wiener [15] on the Rh factor has stimulated further interest in the study of multiple antibodies in syphilis. He has shown that two antibodies are produced in the Rh-sensitized mother: the bivalent antibody (agglutinin), which is retained by the intact placenta, and the univalent antibody (glutinin), which passes through the intact placenta and is responsible for erythroblastosis in the fetus. The latter antibody has the capacity to fix complement.

In the comparison of titers of reagin antibody in adequately treated syphilitic mothers and in their normal fetuses, it has been observed that a similar separation of univalent and bivalent antibodies seems to be effected. In the complement fixation tests for syphilis (detecting univalent antibodies) similar titers of reagin are found in the mother and in the fetus. In the flocculation tests (detecting bivalent antibodies) the level of reagin antibody titers in the infant is minimal as compared with that in the mother.

15. Wiener, A. S.: Rh Factor in Immunological Reactions, Ann. Allergy **6**:293 (May-June) 1948.

In a recent study,[16] the data in the accompanying table were presented, demonstrating comparative titers in mother and fetus, in Kahn units.

Thus it is apparent that two varieties of antibodies, the univalent and the bivalent, may be produced in syphilitic infection. In syphilotoxemia (the passive transfer of reagin antibody to nonsyphilitic offspring of syphilitic mothers), the univalent antibodies predominate. In true prenatal syphilis both varieties of antibodies may be found in similar amounts. Furthermore, this observation serves to explain why maternal reagin in the infant's blood has always been more readily detected by complement fixation than by flocculation technics. In his textbook on the treatment of syphilis, Moore[17] was unable to account for the fact that 113 of 292 normal offspring of syphilitic mothers gave positive complement fixation tests for syphilis, whereas only 8 of a similar group of 158 infants gave positive flocculation reactions. These facts are now explainable on the basis of these newer concepts of two antibodies—the univalent complement-fixing antibody, which readily passes through the intact placenta, and the bivalent flocculation antibody, which does not.

CHEMICAL NATURE OF SYPHILITIC ANTIBODIES

A discussion of the chemical nature of antibodies in syphilis must, of necessity, be limited to the consideration of the reagin antibody. The study of the chemistry of the specific antitreponemal antibody has not been touched on and must remain a problem for the future. Although the exact chemical composition of the reactive substance in serologically positive serum has not yet been determined, recent physicochemical studies have focused attention on certain fractions of serum globulin.

Neurath and his co-workers[18] succeeded in fractionating syphilitic serum into serologically reactive globulin fractions. Their preliminary work dealt with the fractions precipitated with varied concentrations of ammonium sulfate. Increased serologic activity was discovered in globulin fractions precipitated with low concentrations of the salt. That portion of serum precipitated with higher concentrations showed little or no serologic activity. In the crude albumin fraction remaining in solution there was complete absence of serologic activity.

16. Rein, C. R.; Weiner, A. S., and Speiser, M.D.: Unpublished data.

17. Moore, J. E.: The Modern Treatment of Syphilis, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1947, p. 486.

18. Neurath, H.; Volkin, E.; Erickson, J. O.; Craig, H. W.; Putnam, F. W., and Cooper, G. R.: Biologic False Positive Reactions in Serologic Tests for Syphilis: I. Preparations and Properties of Serologically Active Globulin Fractions Obtained by Fractional Precipitation with Ammonium Sulphate, Am. J. Syph., Gonor. & Ven. Dis. **31**:347 (July) 1947.

Further work of these investigators [19] dealt with the fractionation of serum by isoelectric precipitation with dilute hydrochloric acid. In these studies it was shown that the euglobulin precipitate so obtained contained 50 per cent of the total reagin antibody titer of syphilitic serum. Considering that this fraction represents approximately 7 per cent of the total serum protein, it is seen that a sevenfold concentration of reagin antibody was effected.

Employing the Tiselius apparatus, these workers electrophoretically analyzed the euglobulin fraction and found that 50 per cent of it consisted of gamma globulins. This amount represents only 13 per cent of the total serum gamma globulin. It is obvious, therefore, that only a fraction of the total gamma globulin is serologically active. This observation is fully in accord with Eagle's [20] more direct measurement of antibody protein. Eagle calculated that it required a minimum of 0.3 mg. of reagin protein per hundred cubic centimeters of serum to effect a positive flocculation test. This figure represents merely one twenty-thousandth of the total serum protein. Thus the physiochemical properties of the reactive substance point clearly to the conclusion that the reagin of syphilitic serum, like antibodies in general, is a relatively specifically reactive protein associated with gamma globulin.

In contrast to the accepted concept of the protein nature of the reactive substance, there is some evidence pointing to the association of reagin antibody activity with mineral changes in the serum of syphilitic patients. Pierce and Breazeale [3] have shown that calcium is removed from serum with a positive reaction when the latter is treated with either sodium zeolites or lipidal antigen. In some preliminary experiments [21] it has been possible for one of us (C. R. R.) to produce positive flocculation tests for syphilis on the addition of dilute solutions of calcium and strontium salts to negative serums.

In serologic studies on skeletal remains of archeologic specimens of bone 1,000 to 10,000 years old, Breazeale [22] directed further attention to this concept. Using saline extracts of the marrow of such bones as one would employ serum, he obtained positive reactions in flocculation and

19. Erickson, J. O.; Volkin, E.; Craig, H. W.; Cooper, G. R., and Neurath, H.: Biologic False Positive Reactions in Serologic Tests for Syphilis: II. Preparation and Properties of Serologically Active Serum Euglobulin Fractions Obtained by Isoelectric Precipitation, Am. J. Syph., Gonor. & Ven. Dis. **31**:374 (July) 1947.

20. Eagle, H.: Reactions Between Lipoids and Antibodies: I. The Isoelectric Point and Composition of the Aggregates Obtained on Adding Beef-Heart Lipoid to Syphilitic Serum, J. Immunol. **29**:467 (Dec.) 1935.

21. Rein, C. R.: Unpublished data.

22. Breazeale, E. L.: Personal communication to the authors.

in complement fixation tests with 10 per cent of 80 such specimens. In addition, polarographic studies showed a definite shift in the sodium-calcium ratio between the extracts reacting positively and those giving no reaction. While these studies are of extreme interest, particularly with regard to the antiquity of the disease syphilis, it has not been adequately shown that the positive reactions are the sole result of mineral changes. The presence of possible protein substances in the extracts was not determined. Thus, pending further confirmation of the role of minerals in positive serologic reactions, the preponderance of evidence points to the protein nature of syphilitic reagin antibody.

INHIBITOR SUBSTANCES AND THEIR APPLICATION IN SEROLOGIC TESTS

It is a well established fact that positive serologic reactions for syphilis are obtainable in serums from human beings with nonsyphilitic diseases, as well as in those from normal persons. Attempts have been made to differentiate chemically and immunologically the reactive substance of syphilis from that of nonsyphilitic conditions. For this purpose numerous "verification procedures" have been used, including those of Hecht,[23] Wassermann,[24] Witebsky [25] and Kahn.[26] None of these methods have been able to distinguish consistently between true positive and false positive serologic reactions. In recent years, efforts in this direction have been made with the employment of substances obtained from human serum which inhibit serologic reactions.

Rein and Elsberg [27] found that the flocculation of lipidal antigens by serums of syphilitic persons was inhibited on the addition of fresh

23. Hecht, H.: Zum Wesen der Wassermannschen Reaktion, Prag. med. Wchnschr. **39**:316, 1914; Eine neue Flockungsreaktion bei Syphilis, Deutsche med. Wchnschr. **47**:1487, 1921.

24. von Wassermann, A.: Neue experimentelle Forschungen über Syphilis, Berl. klin. Wchnschr. **58**:193, 1921. von Wassermann, A., and Ficker, M.: Reinkulturen der Spirochæta pallida in festem und flüssigem Nährboden, säure uebertragung dieser Kulturen auf Tiere, Klin. Wchnschr. **1**:1101, 1922.

25. Witebsky, E.: Eine Bestätigungsreaktion zur Serodiagnosis der Syphilis, Ztschr. f. Immunitätsforsch. u. exper. Therap. **80**:323, 1933.

26. Kahn, R. L.: A Serologic Verification Test in the Serodiagnosis of Latent Syphilis, Arch. Dermat. & Syph. **41**:817 (May) 1940. Kahn, R. L.; McDermott, E. B., and Marcus, S.: Effect of Temperature on Kahn Reaction, with Serologically Positive Sera of Lower Animals, Am. J. Syph., Gonor. & Ven. Dis. **25**:151 (March) 1941; Effect of Temperature on Kahn Reaction, with Serologically Positive Sera of Human Syphilis, ibid. **25**:157 (March) 1941; Effect of Temperature on Kahn Reaction, with Serologically Negative Sera in Absence of Syphilis, ibid. **25**:162 (March) 1941.

27. Rein, C. R., and Elsberg, E. S.: Are Current Verification Tests of Practical Value in the Serodiagnosis of Syphilis? J. Invest. Dermat. **6**:113 (April) 1945.

unheated normal human serum. No inhibition of the flocculation was noted in serums of nonsyphilitic patients with false positive serologic reactions for syphilis. Heating the fresh serum at 56 C. for thirty minutes completely destroyed the inhibiting effect, and it was postulated that the inhibitor substance was a complement-like material. Use of this thermolabile inhibitor in a "verification" procedure was made in several thousand serums at the Army Medical School. At first the results were exceptionally good, but it was soon discovered that the method had definite limitations. This was particularly evident in cases of false positive serologic reactions in leprosy, wherein most of the reactions were of the syphilitic type.

The most promising advance in the differentiation of the two varieties of reagin antibody has been forthcoming as a result of the physicochemical studies of Neurath and his associates.[28] These workers isolated a thermostabile inhibitor substance which selectively inhibited the flocculation of lipidal antigens by the euglobulin fraction of biologic false positive serum. In syphilitic serum no such inhibition was noticed. Purification of the inhibitor substance has been accomplished, and it has been determined chemically to be related to the lecithin in human serum. The euglobulin inhibition procedure of Neurath makes use of this inhibitor by the comparison of serologic titers of euglobulin buffer mixtures with those of euglobulin inhibitor mixtures. In the case of biologic false positive serum, there is inhibition of serologic activity in the euglobulin inhibitor mixture, as compared with the activity in the euglobulin buffer mixture. On the other hand, in syphilitic serums similar titers are obtained with both mixtures.

These investigators[29] hypothesized the existence of two separate antibodies: the biologic false positive antibody and the syphilitic antibody. A competition exists between the inhibitor substance and the antibody for the antigen. The syphilitic antibody has a greater affinity for antigen than has the inhibitor, whereas the false positive antibody loses out to the inhibitor in the competition for antigen.

We have employed the Neurath test in more than 1,300 serums and have found it to be of decided value as an aid in differentiating nonspecific from true syphilitic serologic reactions. A survey is now being conducted under the auspices of the United States Public Health Service

28. Volkin, E.; Neurath, H.; Erickson, J. O., and Craig, H. W.: Biologic False Positive Reactions in Serologic Tests for Syphilis: III. Preparation and Properties of Serum Protein Fractions Which Inhibit Biologic False Positive Reactions, Am. J. Syph. Gonor. & Ven. Dis. **31**:397 (July) 1947.

29. Volkin, E.; Neurath, H., and Craig, H. W.: Biologic False Positive Reactions in Serologic Tests for Syphilis: IV. Quantitative Aspects of the Inhibition Phenomenon, Am. J. Syph., Gonor. & Ven. Dis. **31**:413 (July) 1947.

to evaluate this procedure. Until this study is completed, use of the procedure should be restricted to experimental laboratories.

CONCLUSIONS

1. An attempt has been made to review the present concepts of the nature of antigens and antibodies in syphilitic serum.

2. It has been shown that a multiplicity of antibodies may be produced by T. pallidum.

3. Further investigations directed toward identification of specific antitreponemal antibodies will further enhance the understanding of the true immunology of syphilis.

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SEABATHER'S ERUPTION

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DURING the past twelve years I have had the opportunity to observe persons with an acute form of dermatitis which occurs within a short time after bathing in the ocean. This eruption is characterized by erythematous wheals, which appear within a few hours after exposure and persist for several days, involuting spontaneously. The associated pruritus is at times severe, but it subsides in a few days without giving rise to further difficulty. Because this condition is usually mild and transient in its course, many patients do not consult a physician, or they call their family or hotel physician. Some patients become alarmed concerning the diagnosis, and others have sufficient discomfort to cause them to seek further aid. I have observed 67 patients with a dermatitis sufficiently characteristic to suggest the existence of a common etiologic basis. In each instance there is a history of exposure at one of the beaches, followed usually by itching and the appearance of welts, or inflammatory papules, within a few hours. This eruption occurs predominantly on those parts of the body which are covered by the bathing suit. In some cases it is reported that there is slight itching while bathing in the ocean, but for the most part discomfort is not noted until the patient leaves the water. Usually the itching begins several hours after exposure, frequently at night and often as late as the following day. In children, especially in younger children in whom the eruption is extensive, fever is common, often with an elevation of temperature to 101 or 102 F., and sometimes higher. In spite of the severity of the symptoms, however, the disorder will ordinarily run its course in four or five days, leaving only excoriations as evidence of the preexisting dermatitis.

Patients usually seek the aid of their physician on the day following exposure, and at the end of a twenty-four hour period the dermatitis is well delineated. In children and men who wear only bathing trunks, the lesions will be found predominantly on the covered parts, and they will be more pronounced over the buttocks and about the waist, which are pressure areas (fig. 1). In women, in addition to these locations, lesions will occur on the breasts, under the brassiere of a tightly fitting suit and, some eight or ten years ago, when bathing suits with a rope halter about the neck were in vogue, patients were seen with

a bead of lesions about the neck beneath this part of the bathing suit. In addition to the distribution to covered parts (fig. 2) a few scattered lesions may occur in the armpit, about the neck, on the flexor surfaces of the arms or legs and in the submammary and subgluteal folds. This is particularly true in obese persons.

Fig. 1.—Eruption occurring over the buttocks beneath the bathing trunks, in a boy aged 9.

Individual lesions vary in size from 5 to 15 mm. in diameter in different patients; they are usually uniform, and all appear to be in the same stage of development. Close inspection reveals that the vast majority of the lesions are follicular, and what appears to be a central punctum is, in fact, a slight serous crust which is not infrequently removed by rubbing or scratching, after which it may be replaced with

a hemorrhagic crust. Repeated microscopic examination of these small serous crusts has not revealed foreign bodies or organisms of any type.

At various times material has been removed for histologic examination, and the picture is always that of an acute, toxic, inflammatory process. In those cases in which the tissue was cut in serial sections and examined, it was found that the center of the inflammatory reaction

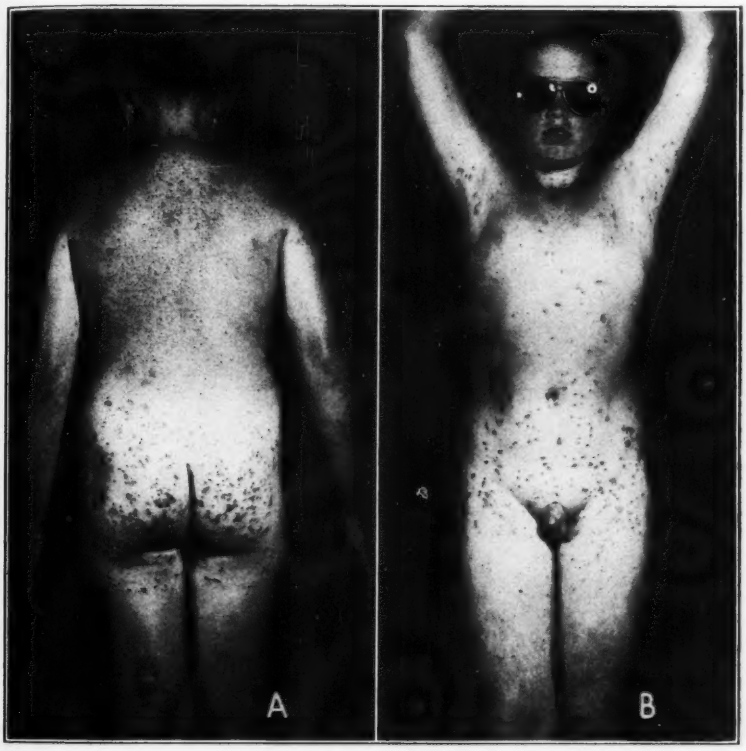

Fig. 2.—Eruption occurring (*A*) predominantly on covered parts over the buttocks; distribution (*B*) of eruption on anterior surface with scattered papules in the axillas and over the abdomen and neck. (Dr. A. Buist Litterer).

occurred at a hair follicle and here, at the surface of the epidermis where the small, serous crust is clinically discernible, there are changes characterized by a break in continuity of the epidermis, with a slight serous exudate and definite intraepidermal vacuolization (figs. 3, 4 and 5). This occurs in both the basal cell and the prickle cell layer, being more pronounced in the latter location. In the corium the

edematous process is less pronounced, but it extends over a wider area. The blood vessels are dilated in the subpapillary region, and this condition extends well down into the corium. Although this edematous process is extreme, further changes other than edema are not observed in the blood vessel walls. There is a well defined inflammatory infiltrate, which in the corium is predominantly perivascular and extends up to enclose the hair follicle. Although round cells predomi-

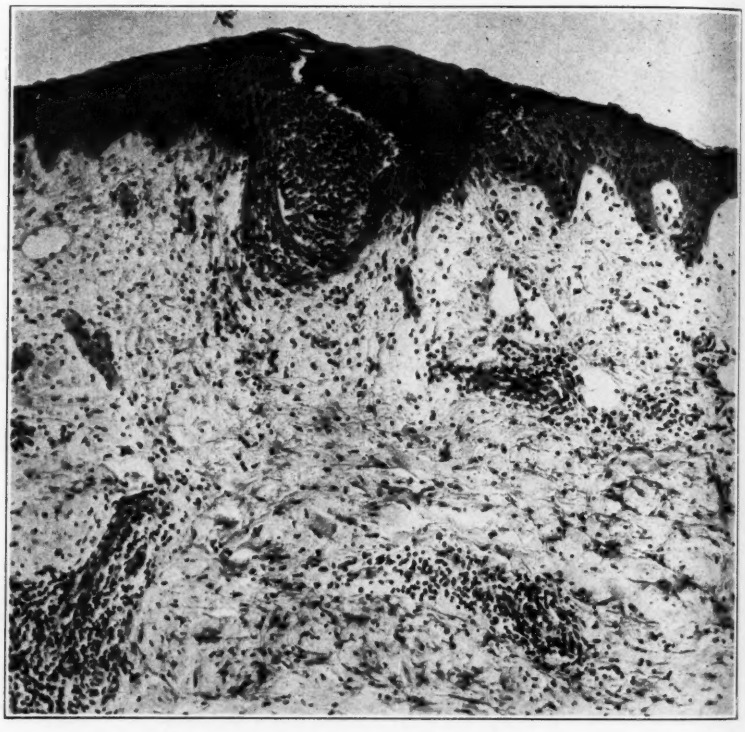

Fig. 3.—Section showing acute, toxic, follicular reaction, with perifollicular infiltration.

nate, many polymorphonuclear leukocytes are present; in the deeper part of the section, eosinophilic cells are observed. In two lesions which were examined in serial section, the histologic changes were identical, the center of the process being each time follicular. This picture has been observed in sections previously examined. Material for examination has been obtained twenty-four hours after exposure and forty-eight hours after exposure, with little difference in the microscopic observa-

tions. In no case has any foreign body or parasite been demonstrated in any material submitted for histologic examination.

The disorder is so characteristic, from the clinical standpoint, as to present little difficulty in diagnosis. The injury to the skin caused by contact with the Portuguese man-of-war (Physalia arethusa), occurs on exposed parts.[1] A stinging sensation begins immediately and is much severer than is the case with the eruption being described.

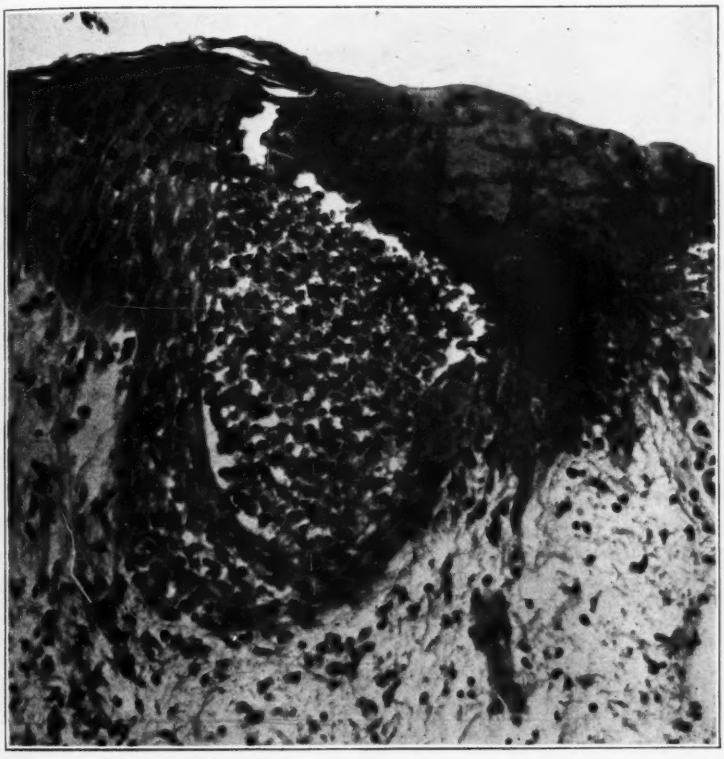

Fig. 4.—High power magnification of portion of figure 2 reveals serous crust at side of hair follicle.

It is interesting to note, however, that the severe dermatitis which is produced by contact with the tentacles of the Portuguese man-of-war is often associated with a few outlying papular lesions similar to those which occur beneath the bathing suit in seabather's eruption. I have found no reference to histologic study of the dermatitis produced by

1. Crutchfield, E. D.: Dermatitis from Portuguese Man-of-War, Arch. Dermat. & Syph. **12**:72-75 (July) 1925.

Physalia; yet the clinical picture has been described and reported several times. Contact with various coelenterates, and in particular Physalia, results in a severe dermatitis due to some toxic material which is extruded by the small stinging cells (nematocysts) on the trailing tentacles (dactylozooids) and gastrozooids of this coelenterate. The nature of the toxic material ejected by the nematocysts is unknown.[2]

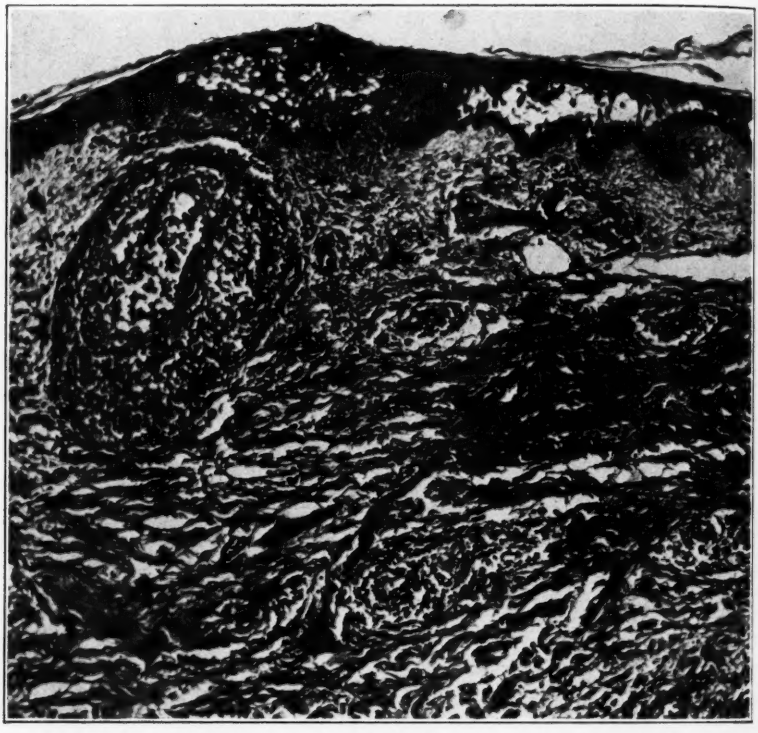

Fig. 5.—Photomicrograph exhibiting intraepidermal vacuolization and edematous reaction in the corium.

A dermatitis has been reported as resulting from contact with hydroids[3] and from contact with coral.[4] In both cases, however, the eruptions

2. Hyman, L. H.: The Invertebrates: Protozoa Through Ctenophora, New York, McGraw-Hill Book Company, Inc., 1940, p. 391.

3. de Oreo, G. A.: Dermatitis Venenata Resulting from Contact with Marine Animals (Hydroids), Arch. Dermat. & Syph. **54**:637-649 (Dec.) 1946.

4. Levin, O. L., and Behrman, H. T.: Coral Dermatitis, Arch. Dermat. & Syph. **44**:600-603 (Oct.) 1941.

occurred on the exposed parts of the body. Seabather's eruption occurs predominantly on covered parts, which immediately serves to differentiate it from the foregoing dermatitis. The appearance of lesions immediately after bathing, the large number which occur at the same time and the fact that no visible organisms have been observed will serve to exclude insect bites, which the lesions themselves so closely resemble.

Since the disorder is self limited and never persists for longer than seven to ten days, treatment is palliative and usually poses no problem. In those cases observed during the past two years, a good measure of relief has been afforded by the antihistaminic drugs. Prior to that, Weber,[5] while stationed at Miami Beach, Fla., observed many cases of seabather's eruption in army personnel of the Army Air Force Regional Station Hospital, during July 1944. He reported that the intravenous administration of calcium gluconate gave the patient surprising relief within four to six hours following injection. Thomas,[6] in a report concerning stings from jellyfish and Portuguese man-of-war, first mentioned this eruption which occurs in seabathers and which occurs characteristically beneath the bathing suit. It had been previously observed by, and is a well recognized clinical picture to, physicians who practice along the lower east coast of Florida.

The problem involved, then, is to determine the cause of this eruption, in order that a method to prevent exposure may be devised. Here a number of difficulties ensue. First, it is impossible to determine when these attacks will occur. A review of records of 67 patients indicates that exposure may occur as early as March 15, and from that time on to approximately September 1. There was 1 single sporadic case observed in October. Such cases are not the rule, however, and when 1 patient is seen it is likely that more will present themselves within the next one or two days, and that hundreds, and sometimes perhaps a thousand persons have been exposed on a single day. My records indicate that cases occurred over a period of nineteen days during one epidemic and over a period of fourteen days during a second attack. For the most part, however, they will occur on a single day and then further cases will not be encountered for months. Fortunately, the condition occurs infrequently; some years it does not put in its appearance at all. In other years two or three separate attacks have been observed. Unfortunately for purposes of investigation, it has been impossible to predict when an attack will occur, and usually additional cases will not be encountered after the onset of a current attack.

5. Personal communication to the author.

6. Thomas, E. J.: Jelly Fish and Portuguese Man-of-War Stings, J. Florida M. A. **26**:83-87 (Aug.) 1939.

Correspondence with dermatologists around the Gulf Coast and up to the Carolinas suggests that seabather's eruption is confined perhaps to Florida waters and is most common along the lower east coast. Mount [5] and Wilson [5] have both observed cases which are similar to, or identical with those already described. Wilson reported that he has seen the eruption occurring over a period of three weeks on four occasions during the past several years. He first experienced the condition himself after swimming at Cortez Beach along the Gulf Coast. About one hour after he came out of the water a severe, papular, urticarial eruption occurred over all the covered parts. Both Wilson and Mount reported that some of their patients had observed small jellyfish in the water at or about the time of their exposure, and a review of my case histories reveals 5 instances in which patients have noticed jellyfish in the water at the time they were in bathing. I, personally, have not observed cases which have originated on the west coast of Florida, and all the patients in my series were exposed off the lower east coast, with the exception of one, who reported that he had gone swimming in the Eleuthera Islands. This is in the Bahamas group, and I have observed an identical eruption at Bimini, on the east side of the Gulf Stream. Alan Brown,[5] at Jacksonville, Fla., reported 3 cases observed in his office in the past ten years. One bather was exposed at Ponte Vedra, a second at Palm Beach, Fla., and a third at Fort Lauderdale. All gave a history of wearing a wet bathing suit for an hour or more after swimming in the ocean, and the eruption was confined to covered areas.

Seabather's eruption should not be confused with previous cases which have been reported under the name of "swimmer's itch." This is a condition which occurs only in fresh water, and it may involve any exposed part, frequently occurring on the hands and feet. It has been adequately studied and proved to be due to Schistosoma cercariae which penetrate the skin.[7] It is believed that seabather's eruption is due to some living, microscopic organism, in the nature of nematocysts from some form of coelenterate which is free-floating, or perhaps from some unicellular organism which is equipped with similar stinging apparatus capable of inflicting injury when provoked by an adequate stimulus. Under suitable conditions, which are achieved beneath the bathing suit by pressure, change in temperature or the evaporation of water, nematocysts or other organisms, may be discharged and produce sufficient injury to cause itching, stinging and the subsequent dermatitis.

7. (*a*) Cort, W. W.: Schistosome Dermatitis in the United States (Michigan), J. A. M. A. **90**:1027-1029 (March 31) 1928. (*b*) McMullen, D. B., and Beaver, P. C.: Studies on Schistosome Dermatitis: The Life Cycles of Three Dermatitis-Producing Schistosomes from Birds and a Discussion of the Subfamily Bilharziellinae (Tematoda; Schistosomatidae), Am. J. Hyg. **43**:128-154 (Sept.) 1945.

Studies to determine the nature of the injurious agent have, to date, been without result. Examination of the bathing suits worn by persons in whom the eruption has developed has yielded no clues. Microscopic studies on the skin disclose no penetrating parasites. Preliminary examination of samples of seawater and of bathing suits which had been worn by patients has revealed no agent which appears capable of producing the dermatitis. It has thus far been impossible to anticipate the attacks and examine water at the time the injurious agent might be present. An attempt to cause a similar dermatitis by applying free-floating nematocysts suspended in seawater to the skin with a woolen stockinet produce no injury. If such nematocysts are the causative agent, it is difficult to assay the factors which will provide adequate stimulus and yet prevent premature discharge of the nematocysts prior to their application to the skin.

CONCLUSION

A heretofore unreported dermatitis has been observed in persons who bathe in the ocean on the lower east coast of Florida. This condition appears at infrequent intervals, and its occurrence is unpredictable. The agent which causes the eruption is yet to be determined.

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ABSTRACT OF DISCUSSION

DR. LOUIS B. MOUNT, St. Petersburg, Fla.: Dr. Sams has appropriately termed the condition that he has described "seabathers' dermatitis." Almost any other name would have caused more confusion in the dermatologic nomenclature.

The dermatosis seems to be confined to the east and west coasts of Florida and more specifically to the southern half. Its occurrence is unpredictable, and it is also my experience that when it does appear most of the patients present themselves within ten to fourteen days. Then no more are seen until perhaps the following year, or two or three. The diagnosis is not difficult because the eruption is predominantly under the bathing garment. It is quite uncommon to find lesions in other areas, although, as Sams has stated, once in a while they do occur. To the uninitiated it might appear to be a papular urticaria, and it is often so diagnosed. Dr. Lunsford in his talk about flea bites made a similar remark. I have been asked if the disease is like the swimmer's itch due to the schistosome. Dr. Sams's description gives the answer—no! It is also quite different from the dermatitis due to bathing trunks and/or shorts. One interesting and perhaps valuable fact brought to my attention by several persons who have had seabather's dermatitis is that in others of their party, who were in bathing at the same time but who showered themselves well almost immediately after coming out of the ocean, an eruption did not develop. Dr. Sams has stated that one can only speculate as to the cause of the dermatitis. When he wrote some time ago to ask my idea of what produced the lesions I agreed with him that it probably was some of the Coelenterata, a phylum of invertebrates which includes the corals, hydroids and jellyfish, and more specifically some small form of the latter. Old fishermen on the west coast of Florida are positive that jellyfish produce the "itch," as some of them call it. With a fine meshed scoop they can

demonstrate the presence of coelenterates in large numbers during the period when cases of the dermatitis are appearing.

We are indebted to Dr. Sams for calling attention to this hitherto undescribed dermatosis and for furnishing as much information about it as is now available.

DR. FREDERICK G. NOVY JR., Oakland, Calif.: I would like to report on a type of swimmer's dermatitis observed in waters around the island of New Guinea. This dermatitis occurred usually several miles off shore in waters free of Portuguese man-of-war. The organism causing the dermatitis was localized to shifting areas of the sea, because swimmers would contract the dermatitis in one place while others a short distance away would be free of it. There was an immediate reaction on diving in the water. It was like diving into a bed of nettles. Papular urticarial lesions developed, which lasted from about two to fourteen hours. The distribution of the eruption differed from that described by Dr. Sams. In the cases observed near New Guinea it did not occur on covered surfaces, for there were no covered surfaces.

DR. SAMUEL AYRES JR., Los Angeles: Last summer I saw an instance of this dermatitis which was the first I had ever seen. The patient had just flown in from Florida. The eruption was the same as that which Dr. Sams described, covering the bathing trunk area. Exposure had occurred two or three days' previously. This man had been bathing on the Gulf Coast and stated that six or eight persons of his party had such an intense itching that they had to get out of the water quickly. He stated that at the time this occurred they were having the "red tide." Has Dr. Sams given thought to the organism producing that phenomenon as a possbile cause of the dermatitis?

DR. LOUIS WINER, Beverly Hills, Calif.: I have examined histologic sections of several biopsies of swimmer's itch. The organism was found with difficulty in the skin section. The skin microscopically revealed a degenerative process of follicular epidermis with a tendency to vesiculation. Islands of round cells and polymorphonuclear infiltration observed in the cutis were not unlike those apparent in histologic study of insect bites.

DR. JOHN BELISARIO, Sydney, Australia: I enjoyed Dr. Mount's discussion of this interesting paper. For a number of years Australian physicians have occasionally observed a similar condition of a person going bathing and experiencing a stinging sensation, which may come on while he is in bathing or afterward. The outbreak is arrested or prevented by immediate showering after coming out of the water. The lesions are quite similar. They vary from macules to papules. They do occur on exposed surfaces but are more troublesome on the covered surfaces. As a point of interest, it has been noticed that attacks occur after a storm, when jellyfish are broken up and rotting. A number of years ago in a small town called Eden I got in among some myself. It was not a pleasant sensation. I would be interested to know whether you have noticed a connection between stormy, rough weather and outbreaks of the eruption in this country.

DR. EUGENE TRAUB, New York: Dr. Belisario mentioned storms and the washing ashore of jellyfish, man-of-war and other forms of sea life. Would it not be possible under such circumstances that the bather would soak up enough material in his suit to hold it tightly against his skin sufficiently long to produce the dermatitis? Has patch testing been done with samples of water taken close to shore directly after rough weather? Also, it might be feasible to make extracts of different types of jellyfish and man-of-war to test this material, unless this has been proved valueless already. Immediately after an eruption has occurred, has testing been done with the trunks that were worn?

DR. HARRY ARNOLD, Honolulu, Hawaii: In Honolulu these lesions have never been observed, though there are Portuguese man-of-war in comparative abundance, and ample surf, so that if their tentacles could be broken up by storms, the results of it should be seen—and they are not. I have never observed anything even remotely approximating the condition described by Dr. Sams.

DR. W. M. SAMS, Miami, Fla.: I have talked with many physicians regarding this dermatosis during the past twelve years, and most of the questions presented have been brought up at one time or another. It is our present intention to examine water from the beaches by collecting plankton samples at weekly intervals throughout the season. When seabathers' eruption makes its first appearance, daily examinations can be carried out. Anyone who has examined the water from the ocean under the microscope, and has observed the many organisms which are present, will realize that this is a problem for the marine biologist. It is also planned to study the dermatitis produced by contact with the tentacles of the Portuguese man-of-war. The histologic picture has not been described in the literature, and its comparison with the present disorder may give some additional information. The "red tide" to which Dr. Ayres referred has been studied, and a small unicellular organism was found to be a cause of the discoloration of the water (Davis, C. C.; Gymnodinium Brevis sp. Nov., A Cause of Discolored Water and Animal Mortality in the Gulf of Mexico, *The Botanical Gazette*, **109**:3 [March] 1948). The reason for the sudden tremendous increase in these organisms has not been determined. One explanation offered is the decreased salinity which may occur at certain times due to heavy rainfall and rapid drainage of fresh water from the adjacent peninsula. Three different histopathologists have examined sections from several patients. In 2 cases, serial sections were cut through the papules concerned. The pathologists found nothing which in their opinion could be a parasite. I appreciate Dr. Belisario's discussion and the information which he brings concerning an eruption of similar character from that part of the world. As far as has been determined, the dermatosis has no definite relation to on-shore and off-shore breezes, but many local residents have reported an usually large amount of seaweed on the beaches or in the water when the eruption developed. There is seldom a heavy surf off the east coast of Florida, and the Portuguese man-of-war is present in variable numbers throughout the year. It is hoped that further investigation will yield more information regarding this interesting dermatosis.

PEMPHIGUS ERYTHEMATOSUS

FRANCIS EUGENE SENEAR, M.D.
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AND
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IN 1926 one of us, with Usher,[1] made the first formal report on a group of cases, the first examples of which had been demonstrated by Ormsby and Mitchell before the Chicago Dermatological Society in 1921. The paper was entitled "An Unusual Type of Pemphigus, Combining Features of Lupus Erythematosus" and described 11 cases, 5 of which had been observed by one or both of the writers.[1] It was then stated that the peculiar clinical features of the dermatosis made it difficult to determine beyond dispute its proper place among cutaneous disorders. It was suggested, however, that there were two possibilities that must be considered—either that manifestations resembling lupus erythematosus can occur as an atypical feature of pemphigus or that we were dealing in this instance with a syndrome in which pemphigus occurs in combination with lupus erythematosus, a common etiologic factor being responsible for the development of both disorders. At that time the writers believed that the latter conception was the more probable.

Subsequently there have been many case presentations and a number of papers dealing with what had come to be known as the Senear-Usher syndrome. From the time of the discussion following the presentation of the original paper, a lack of unanimity as to the status of the disorder was apparent, the major portion of the controversy centering about the question whether these cases were examples of lupus erythematosus with bullous lesions or of pemphigus. There was also considered the possibility that cases of this type might constitute an entity.

REVIEW OF THE LITERATURE

To illustrate the developments which have taken place in the interpretation of these cases, we have selected in chronologic order from the literature a number of statements by various observers. Not all of these are given in toto, but we believe that in no instance is the meaning obscured by the omissions.

1. Usher, B., and Senear, F. E.: An Unusual Type of Pemphigus, Combining Features of Lupus Erythematosus, Arch. Dermat. & Syph. **13**:761 (June) 1926.

Wise [2] stated: "To illustrate that this group should not be called pemphigus, I will briefly recite an experience with one case." He described the case of a woman who had on her face and body an eruption diagnosed clinically and histopathologically as lupus erythematosus; pemphigoid lesions soon developed on various parts of her body. "We are not justified in assuming that these adventitious bullae are those of true pemphigus. They resemble pemphigus, but, with the exception of being bullous lesions, they do not correspond to the clinical picture of that disease."

On the same occasion Mook [3] remarked: "I think we all have the same difficulty in the early diagnosis of these cases. On the first examination our impression is that they are lupus erythematosus with a few pemphigoid lesions. . . . It has been our experience that after five or six weeks' observation and study of the patients, we have changed our diagnosis two or three times, but in all of them our final conclusion has been that the cases are more like pemphigus than lupus erythematosus."

Wise [4] made this statement: "The point I wish to stress is this: I believe that lupus erythematosus, when it simulates pemphigus, erysipelas, seborrheic dermatitis, erythema multiforme, dermatitis herpetiformis and what not, is still only lupus erythematosus.

"Once in a while, we notice an inadvertent slip on the part of those who refer to the Senear-Usher type of lupus erythematosus, instead of the Senear-Usher type of pemphigus." Wise then stated that the case presented by him (used as case 4 in the original article by Senear and Usher [1]) was a form of benign pemphigus, while the second case presented by him (case 7 in the same article), although at the time of demonstration considered as possibly one of "developing pemphigus," proved to be lupus erythematosus; pemphigus did not develop in the patient. In this paper on "Lupus Erythematosus Bullosus or Pemphigoides," Wise considered that 5 of the 11 cases included in our original report were examples of "benign" pemphigus, while 6 were examples of lupus erythematosus disseminatus.

Gilman,[5] in reporting 1 case and adding 13 further cases culled from the American literature, stated that "there appears to be a toxic, or at least an abnormal, metabolic state that occasionally induces synchronously the morbid changes of at least two, and possible three, different dermatologic complexes: lupus erythematosus, pemphigus and

2. Wise, in discussion on Senear and Usher.[1]

3. Mook, W., in discussion on Senear and Usher.[1]

4. Wise, F.: M. J. & Rec. **134**:227, 1931.

5. Gilman, R. L.: Senear-Usher Syndrome: Dermatosis Combining Features of Lupus Erythematosus and Pemphigus, Arch. Dermat. & Syph. **24**:84 (July) 1931.

possibly seborrheic dermatitis." Later on in the same paper, he stated: "While it is possible to be didactic and to denominate each of the 11 cases as a single clinical entity, the alternative, namely, to say that all of them are lupus erythematosus with added features of pemphigus, is justified because the combination of symptoms has occurred so often; that is, such a frequent combination has significance and is not coincidental." And still later we find: "The creation and insistence of the Senear-Usher concept of the cases described will be useful and will serve as a midway station, or, as the original authors suggested, a state of toxic eruption transitional between lupus erythematosus disseminatus and pemphigus."

Mook, Weiss and Bromberg,[6] reporting 13 cases of lupus erythematosus disseminatus in an article in 1931, stated that 3 of them were of the "Senear-Usher type of lupus erythematosus." The patient described in case 13 in their series is the same patient whose condition was described in case 2 of the original report.[1] Mook had apparently changed his opinion from that which was stated about five years before, and he and his collaborators commented here that "it is striking that in all 3 of the cases of the Senear-Usher type, no evidence of serous involvement was found." This fact, it seemed to them, was the only serious consideration against classing the latter type of case as disseminated lupus erythematosus. They stated, "we have gained the impression that Senear and Usher regard their cases as atypical pemphigus, while we are inclined to class them as lupus erythematosus disseminatus with pemphigoid features."

Woodburne[7] believed that "it might be well to exclude cases of lupus erythematosus disseminatus with bullous lesions in which microscopic examination substantiates this diagnosis from the group of Senear-Usher pemphigus and to limit this group to cases showing the pathologic process which seems to be identical except for degree in the cases examined by Finnerud, Gilmer and me."

In the discussion of cases presented by Traub and Wright, Wise[8] remarked that "a number of these cases are difficult of interpretation, but the majority are actually lupus erythematosus with pemphigoid lesions, in other words, disseminated lupus erythematosus pemphigoides. It would be interesting to find out, if possible, what the final results are in these cases. Is the outcome pemphigus, or is the outcome death due to lupus erythematosus disseminatus? . . . The consensus

6. Mook, W. H.; Weiss, R. S., and Bromberg, L. K.: Lupus Erythematosus Disseminatus, Arch. Dermat. & Syph. **24**:786 (Nov.) 1931.

7. Woodburne, A. R.: Senear-Usher Pemphigus, Arch. Dermat. & Syph. **26**:671 (Oct.) 1932.

8. Wise, F., in discussion on Traub, E., and Wright, C. S.: Lupus Erythematosus (Bullous type) or Senear-Usher Pemphigus, Arch. Dermat. & Syph. **27**:714 (April) 1933.

in New York is the one which was expressed by Dr. MacKee, namely, that most of these are cases of lupus erythematosus. . . . I still believe that cases which do not present typical pemphigus, with its constitutional symptoms, loss of weight and, above all, pathologic apprehension, indicate that we are dealing with lupus erythematosus per se, which has become disseminated and in which the edema has caused an eruption of bullous vesicles, rather than true pemphigus."

Mook continued the discussion by reiterating the foregoing opinion that these cases should be classified as lupus erythematosus.

Chiale,[9] on the basis of personal observations and a study of the literature, expressed the belief that the definition of Senear and Usher, "pemphigus of a rare type, combining features of lupus erythematosus," corresponded closely with the clinical picture, and he commented that this form of disease seems to be not so much the expression of a transition or combination between pemphigus and lupus erythematosus as a variation of the classic clinical picture of pemphigus vulgaris, from which it may become distinguishable in the future, once its clinical significance is better known.

Taussig [10] reported a case under the title, "Senear-Usher Syndrome —a Variety of Lupus Erythematosus," and concluded that his patient had lupus erythematosus and that the syndrome is a form of lupus erythematosus and is not a disease entity. He approved the suggestion of Wise that the name "lupus erythematosus pemphigoides" be used. In the discussion following this paper, Ormsby considered that Taussig's case was one of lupus erythematosus with a complicating bullous eruption. He further stated that since the original report a number of cases had been reported, some of which were pemphigus erythematosus, while others were either ordinary lupus erythematosus with bullous lesions or lupus erythematosus disseminatus. Wise then reiterated the opinion which has already been quoted, that some cases are lupus erythematosus with bullous lesions and that others are not. He repeated his belief that some of the cases described in the original report were lupus erythematosus pemphigoides. Taussig, in closing the discussion, stated his belief that several unrelated conditions had been grouped under the Senear-Usher syndrome.

Ormsby presented 2 cases before a meeting of the American Dermatological Society on June 10, 1933, and in the discussion which followed Wise [11] remarked: "I wish again to call attention to the mistake of calling these cases the Senear-Usher type of pemphigus instead of the Senear-Usher type of lupus erythematosus. I agree

9. Chiale, G. F.: Gior. ital. di dermat. e sif. **74**:1487, 1933.

10. Taussig, L.: Senear-Usher Syndrome: Variety of Lupus Erythematosus, Arch. Dermat. & Syph. **27**:498 (March) 1933.

11. Wise, F., in discussion on Ormsby, O. S.: Pemphigus, Atypical (Schmidt Type), Arch. Dermat. & Syph. **29**:149 (Jan.) 1934.

with Dr. Ormsby and his pupils that at least some of these cases are probably mild or atypical, or benign pemphigus, but that others are lupus erythematosus with vesicles or bullae."

In closing, Ormsby stated that "there is no doubt in my mind that the 2 cases presented today are cases of atypical pemphigus. I am also sure that some others are cases of disseminated lupus erythematosus. At present the question cannot be settled as to whether or not this is a disease sui generis."

Comel [12] reported 2 cases, study of which he stated confirmed the original conception of Senear and Usher of a rare form of pemphigus combined with the signs of lupus erythematosus.

As an indication that the confusion experienced in this country is felt elsewhere, we may quote Proppe [13] to the effect that "the classification of the Senear-Usher syndrome, which has assumed increasing significance in recent years, is also as yet entirely uncertain." He questioned whether the cases represented lupus-erythematosus-like eruptions during the course of atypical pemphigus or whether they represented a toxic cutaneous eruption, a transition form between lupus erythematosus and pemphigus.

Richter [14] reported a case in which "lupus erythematosus existing for some years had eventually been followed by an eruption of bullae on the body and by a syndrome, the clinical appearance of which suggested the diagnosis of pemphigus foliaceus." In his discussion of the topic, Richter suggested that there may be in such cases a coexistence of lupus erythematosus and pemphigus, with a single etiologic agent being responsible.

In reporting a case, Gray [15] expressed his belief that pemphigus foliaceus and the Senear-Usher syndrome are variations of the same condition, and he suggested that the latter disorder is a localized form of pemphigus foliaceus and not, as some have thought, a form either of seborrheic dermatitis or of lupus erythematosus, nor has it any particular relation to pemphigus vulgaris. Later, in discussing a case presented by Muende, Gray said that "in February, 1938, he showed a case which he had labelled Senear-Usher syndrome, and at the same time a case of pemphigus foliaceus, and he gave some reasons why he thought the two conditions were the same. The Senear-Usher case eventually developed into a complete pemphigus foliaceus. It was clear that their American colleagues had had great doubts about this condition, but opinion in the States seemed to be moving towards pemphigus and away from lupus erythematosus."

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12. Comel: Boll. sez reg. Soc. ital. dermat., sif. **1**:119, 1936.
13. Proppe, A.: Dermat. Ztschr. **77**:251, 1938.
14. Richter, R.: Arch. f. Dermat. u. Syph. **75**:725, 1937.
15. Gray, A. M. H.: Proc. Roy. Soc. Med. **31**:871, 1938, in discussion on Muende, M. B.: ibid. **32**:420, 1939.

In the discussion of a case presented by Eller, Wise [16] remarked: "I should like to agree with Dr. Traub's diagnosis of pemphigus of the Senear-Usher type. Whenever a patient has persistent lesions on the face which resemble lupus erythematosus or seborrheic eczema, distributed in a butterfly fashion, and small bullous lesions on the body which at one time resemble seborrheic eczema, at another time impetigo contagiosa and perhaps at another time dermatitis herpetiformis, a diagnosis of the Senear-Usher type of pemphigus is to be seriously entertained. Unfortunately, histologic examination does not help much in this type of case. . . . Continued observation may result in one or two diagnoses, either bullous lupus erythematosus or a type of pemphigus."

Ormsby,[17] in discussing a case demonstrated by Cornbleet and Cohen, stated: "After reviewing the cases I have observed, together with some recorded in the literature, I feel sure that there is a syndrome presenting symptoms of lupus erythematosus, seborrheic eczema and pemphigus in combination. . . . I have observed several other cases since that time in which the clinical picture is like that under consideration. The subject has been confused in the literature by the recording of cases which were instances either of true lupus erythematosus disseminatus or of ordinary lupus erythematosus with bullae. Typical lupus erythematosus with bullae has long been recognized."

In discussing the same case, Senear [18] said: "There has been much discussion as to whether the condition should be classed as relatively benign pemphigus or as lupus erythematosus; I think, as Dr. Wise brought out, that in some cases presented as instances of pemphigus, the condition belongs in the lupus erythematous group. I am open-minded on this point, but as in some the condition has developed into typical pemphigus vulgaris terminating in death, I think one must concede that in some cases it definitely belongs in the pemphigus group. The clinical picture varies so greatly that in some cases diagnosed as instances of lupus erythematosus the condition really belongs in the pemphigus group."

Wile and Arnold,[19] reporting 6 new cases under the title "The Senear-Usher Syndrome," did not believe "that the evidence at hand is sufficient to warrant any final conclusions as to the classification

16. Wise, F., in discussion on Eller, J. J.: A Case for Diagnosis (Lupus Erythematosus? Dermatitis Herpetiformis? Pemphigus?), Arch. Dermat. & Syph. **37**:670 (April) 1938.

17. Ormsby, P. S., in discussion on Cornbleet, T., and Cohen, D.: Senear-Usher Syndrome, Arch. Dermat. & Syph. **39**:370 (Feb.) 1939.

18. Senear, F. E., in discussion on Cornbleet, T., and Cohen, D.: Senear-Usher Syndrome, Arch. Dermat. & Syph. **39**:370 (Feb.) 1939.

19. Wile, U. J., and Arnold, H. L., Jr.: The Senear-Usher Syndrome: Review of the Literature and Report of Six Cases, Arch. Dermat. & Syph. **40**:687 (Nov.) 1939.

of the Senear-Usher syndrome at this time, except that it does appear to be a definite entity, distinguishable from lupus erythematosus on the one hand and from pemphigus foliaceus and pemphigus vulgaris on the other." In their conclusions they stated that there is increasing belief that "this syndrome is a definite entity which in many respects lies midway between lupus erythematosus disseminatus and pemphigus vulgaris, differing from both diseases principally in the striking tendency to chronicity." In the discussion of this paper Senear remarked: "It is my belief that in the cases in which the typical picture is present, the disease deserves recognition as a clinical entity. The remaining evidence . . . makes me feel that the disorder at present should be considered a form of pemphigus, usually benign, but occasionally assuming the clinical form of pemphigus vulgaris and carrying the fatal characteristics of the latter disease."

Chargin,[20] in his discussion of a case presented by Silver, said: "It is my impression that Senear and Usher originally presented their material with the idea of describing a variety of pemphigus in which no bullae are seen or in which bullae rupture rapidly and produce superficial scaly crusts. The eruption bears a resemblance to seborrheic eczema. True lupus erythematosus with bullae was also included in that syndrome. It seems to me that one should either drop the term or agree to call one condition or the other Senear-Usher syndrome and not apply the name to two diseases that are unalike in their course and from every other standpoint. . . . I think that the Senear-Usher syndrome should be limited to one disease, and I have the impression that the authors meant to apply it to a type of pemphigus."

In concluding the discussion Silver remarked: "What Senear and Usher originally described was an unusual type of pemphigus combined with clinical features of lupus erythematosus. Later on the entire concept was confused, and lupus erythematosus with bullous and crusted lesions was also regarded as characteristic of the syndrome. It has always seemed to me somewhat artificial to combine two totally unrelated diseases, the causes of which are still unknown, in a new syndrome. I think that one can safely dispense with the concept of the Senear-Usher syndrome."

Weiss[21] described the case of a woman who had pemphigus vegetans, and in whom, after a remission lasting four years, there developed typical lesions of the Senear-Usher syndrome and eventually a typical exfoliative dermatitis. He stated: "I think her history shows a definite relation between the Senear-Usher syndrome and pemphigus."

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20. Chargin, L., in discussion on Silver, H.: Pemphigus Erythematodes (Senear-Usher), Arch. Dermat. & Syph. **41**:809 (April) 1940.

21. Weiss, R. S., in discussion on Pemphigus Erythematodes (Senear-Usher Syndrome), Arch. Dermat. & Syph. **42**:714 (Oct.) 1940.

Silver,[22] discussing a case presented by Astrachan, stated: "Senear and Usher described a combination of pemphigus with features of lupus erythematosus (including features of seborrheic dermatitis). Later there appeared in the literature reports of a condition typical of lupus erythematosus with bullous lesions, and this was also called the Senear-Usher syndrome. From then on it was not clear whether the Senear-Usher syndrome was lupus erythematosus, pemphigus or a combination of both. Recently Senear himself admitted the existing confusion and was inclined to consider this condition as a variant of pemphigus."

Touraine and Lortat-Jacob [23] have made an extensive review of the subject under the term *la pemphigoïde séborrhéique* and have discussed the various theories offered as follows: 1. The syndrome is a form of disseminated lupus erythematosus; 2. The syndrome is a form of pemphigus; 3. The syndrome is heterogenous, including some cases of lupus erythematosus and some cases of pemphigus. 4. The syndrome owes its special features to a seborrheic soil. 5. The syndrome is an autonomous entity. They pointed out the frequency with which the syndrome has been confused with pemphigus foliaceus and suggested that previously many cases designated as pemphigus foliaceus may have been examples of the syndrome. These writers placed special emphasis on the seborrheic element and proposed the name *la pemphigoïde séborrhéique,* a designation which for them has the triple advantage of separating this disorder from pemphigus, while pointing out its analogies to that disorder; of emphasing the preponderant part which seborrhea plays in its morphologic aspect and, finally, of corresponding to the clinical description.

Cabré Claramunt and Solduga Castells [24] reported a case under the title of "A Case of Phemphigoide Seborrheique" and stated that theirs is a typical case corresponding to the description given by Touraine and Lortat-Jacob, and they agree that the disorder should be designated seborrheic pemphigoid.

In disagreeing with the diagnosis of lupus erythematosus suggested in a case presented by Bloom, Wise [25] stated that the condition is a peculiar type of pemphigus. Bloom noted that the distribution of the eruption was the only feature resembling lupus erythematosus, and he reported that biopsy specimens taken both from a bulla and from

22. Silver, H., in discussion on Astrachan, G. D.: A Case for Diagnosis (Lupus Erythematosus Disseminatus? Senear-Usher Syndrome?), Arch. Dermat. & Syph. **44**:706 (Oct.) 1941.

23. Touraine, A., and Lortat-Jacob, E.: Ann. de dermat. et syph. **1**:28, 1941.

24. Cabré Claramunt and Solduga Castells, Actas dermo.-sif. **33**:405, 1942.

25. Wise, F., in discussion on Bloom, D.: Pemphigus (Senear-Usher Type), Arch. Dermat. & Syph. **45**:781 (April) 1942.

a crusted plaque showed the features of pemphigus and not of lupus erythematosus.

In discussing a typical case shown by Wieder, Ormsby [26] noted that "this form of pemphigus is recognized generally except by some Eastern colleagues. Their conception is that this condition is lupus erythematosus with bullous lesions. This entity is easily recognized, but it is also known that the condition is different both clinically and histologically from the pemphigus under discussion."

In closing the discussion Wieder said: "Concerning the pemphigus versus lupus erythematosus question, the biopsy in this case definitely rules out lupus erythematosus. . . . The balance of evidence would appear to place pemphigus erythematosus as a comparatively rare clinical variant of true pemphigus, with confusion arising from the difficulty of assigning to pemphigus itself the lesions of the Senear-Usher syndrome resembling seborrheic dermatitis and discoid lupus erythematosus."

In discussing a case presented by Costello, Wise [27] commented that "the concept of a combined and coexisting eruption of lupus erythematosus and Senear-Usher dermatosis has never seemed to me to be based on sound clinical and pathologic findings. I have always maintained that the occasional bat wing eruption resembling lupus erythematosus on the nose and the cheeks is merely a manifestation of pemphigus of nonbullous character, frequently associated with the milder manifestations of pemphigus on the trunk and in the mouth. In such instances, sections from the cheeks show no microscopic evidence of lupus erythematosus. I tried to make this clear in an article entitled, 'Lupus Erythematosus Bullosus or Pemphigoides; Report of Two Cases with Discussion of the Senear-Usher Syndrome.' Unfortunately, my comments in this article have been misquoted."

In response to a query by Costello as to the prognosis in this type of pemphigus, Wise answered that "generally pemphigus vulgaris develops in these patients, and they die of that disease."

Cottini [28] described a case which he regarded as an example of this syndrome and stated that he did not have sufficient opportunity for study of his case to draw conclusions without reservations; he believed that it is possible to state that the Senear-Usher syndrome is, most probably, a special episodic phase of pemphigus, benign in its evolution and sensitive to antipemphigus therapy.

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26. Ormsby, O. S., in discussion on Wieder, L. M.: Pemphigus Erythematodes (Senear-Usher), Arch. Dermat. & Syph. **45**:994 (May) 1942.

27. Wise, F., in discussion on Costello, M. J.: A Case for Diagnosis (Lupus Erythematosus with Superimposed Senear-Usher Syndrome), Arch. Dermat. & Syph. **54**:727 (Dec.) 1946.

28. Cottini, G. B.: Gior. di med. **3**:224, 1946.

Biagini [29] gave a detailed discussion of the syndrome, reported the history of a case and expressed the belief that it is possible for him to confirm the opinion of Chiale that the syndrome is a variant of pemphigus, characterized by seborrheic manifestations, which usually are observed in the early stages of the disease.

De Giorgio [30] reported a case in which he was able to demonstrate a positive Nikolsky sign only in the regions surrounding the erosive scale-crusted lesions, and he concluded that this form of disease is a variation of pemphigus foliaceus or an intermediary form between pemphigus foliaceus and pemphigus vulgaris rather than a variation of pemphigus vulgaris alone.

COMMENT

The foregoing review of pertinent excepts from the literature of the past twenty-two years, reveals that almost from the start there was a difference of opinion as to what constituted what came to be called the Senear-Usher syndrome. For some it was a form of pemphigus; for others, a form of disseminated lupus erythematosus. Others thought that the syndrome was supposed to include both diseases, while still others believed that the condition was a new entity or a disease sui generis. It is also apparent that certain writers altered their opinions as opportunity arose for the study of added cases. As the title of the original paper indicated, it was the opinion of Usher and Senear [1] that the condition had to do basically with a type of pemphigus, although they also postulated that a common etiologic factor might be producing in the same person at one time features of both pemphigus and lupus erythematosus. Wise challenged the latter theory; although it has since been supported by Richter, we believe that in the light of later experience this idea must be abandoned. Wise at the outset was of the opinion that the cases in this group should not be called pemphigus. Later, he expressed the view that some of the cases included in the original report were examples of a benign type of pemphigus, while others were in reality cases of lupus erythematosus. He also called attention to the fact that some observers were inadvertently speaking erroneously of a Senear-Usher type of lupus erythematosus instead of a Senear-Usher type of pemphigus. However, he believed that most of the recorded cases were examples of lupus erythematosus rather than pemphigus. Still later he made the remark already quoted: "Whenever a patient has persistent lesions . . . a diagnosis of the Senear-Usher type of pemphigus is to be seriously entertained." Recently, Wise [31] made the following statement: "In summation, I believe (1) that 'Senear-Usher

29. Biagini, E.: Gior. ital. dermat. e sif. **87**:87, 1946.
30. de Giorgio, A.: Gior. ital. dermat. e sif. **87**:105, 1946.
31. Wise, F.: Personal communication to the authors, Jan. 11, 1949.

pemphigus' or pemphigus erythematodes is a variant of pemphigus vulgaris; (2) that eruptions exhibiting ordinary lesions of lupus erythematosus and concomitant vesicles and bullae are extremely rare; (3) that eruptions showing coincident lupus erythematosus and pemphigus are probably nonexistent."

Mook, who in his discussion of the original article [3] was of the opinion that the cases were more like pemphigus than lupus erythematosus, collaborated with Weiss and Bromberg [6] to write a paper on disseminated lupus erythematosus. They included 4 cases of what they termed the Senear-Usher type of lupus erythematosus, and several years later Mook reiterated his opinion that these cases are lupus erythematosus. Still later, however, Weiss conceded a definite relationship between the Senear-Usher syndrome and pemphigus.

It is thus apparent that in recent years, with the opportunity to study more cases, the previous uncertainty with regard to the Senear-Usher syndrome has become largely resolved, and we believe that there is now general acceptance of the disorder as a variant of pemphigus. This opinion has recently been substantially supported by experience with 3 additional cases which at the outset presented typical clinical pictures of pemphigus erythematosus but which went on to the development of equally characteristic features of pemphigus vulgaris in the patient. In the discussion of a case presented by Becker, the death of the patient resulted within four weeks after the onset of the generalized bullous phase. In the other 2 cases the patients are at present under observation and treatment, both manifesting pemphigus vulgaris as a sequel of pemphigus erythematosus.

The literature is replete with instances in which a diagnosis made originally of lupus erythematosus, impetigo, dermatitis herpetiformis, psoriasis, dermatitis medicamentosa, erythema multiforme, epidermolysis bullosa or eczema was changed to one of pemphigus erythematosus only after some weeks or months of observation. It is not surprising, therefore, that proper classification of the disorder led to disagreement. However, when the clinical picture has developed characteristically there is little difficulty in diagnosis, for, as Stokes remarked after observing 7 examples of this disease, all were thumbprints of each other. It is not necessary to describe again the clinical observations, for they vary but little from those given in the original article by Senear and Usher and in subsequent papers by a number of writers.

We might emphasize, however, in an attempt to eliminate any possibility of further confusion of this disorder with lupus erythematosus bullosus, the following observations: 1. Bullous lupus erythematosus is rare. 2. The usual evolution in cases of pemphigus erythematosus is much slower than that of disseminated lupus erythematosus. 3. Constitutional symptoms are infrequent or absent in pemphigus erythematosus. 4. Tthere are no visceral complications in this disease.

5. Lesions of mucous membrane is relatively frequent in pemphigus erythematosus. 6. There is a lack of leukopenia in this condition. 7. Pemphigus erythematosus has a tendency to spare the extremities, which are sites of predilection in lupus erythematosus. 8. Albuminuria is infrequent. 9. Pemphigus erythematosus occurs with greater frequency in males than does lupus erythematosus. 10. Many cases occur in age groups beyond those usually affected by lupus erythematosus. 11. In a high proportion of cases a positive Nikolsky sign is elicited. 12. Bullae frequently arise on a sound skin. 13. Atrophy is absent. 14. The histologic observations in definite cases are not those characteristic of lupus erythematosus but do present a relatively constant though nonspecific picture. 15. There is frequent response in these cases to treatment directed against pemphigus.

Different writers have emphasized various phases of the disorder. Gray, Vieria, Rubello Jr. and others have believed that the condition should be considered a phase of pemphigus foliaceus. There can be no doubt but that in a number of recorded cases the disorder has finally presented the picture of pemphigus foliaceus (cases of Baer Jr. and Kamin, Goldenberg, Comel, Shaffer, Richter, de Giorgio, Valade and others).

In the experience of Ormsby, Wise, Senear and others the more usual end result has been the clinical picture of pemphigus vulgaris.

Touraine and Lortat-Jacob, and Cabré Claramunt and Solduga Castells lay stress on the seborrheic element in the clinical manifestation, and the first two authors suggest that this condition should be called *la pemphigoïde séborrhéique.*

It is our belief that these differences of opinion result because the clinical observations vary greatly from case to case and because writers have in some instances based their opinions on sound observations, but on too small a number of cases to permit conclusions to be drawn.

The writings of South American dermatologists have acquainted us with an endemic form of pemphigus foliaceus occurring in a special geographic distribution, in São Paulo ad Belo Horizonte, and Vieria had studied 480 cases of this disorder in 1941. It would not be within the scope of this paper to consider this disorder were it not that both Rubello Jr. and Vieria have discussed the relationship of this condition to pemphigus erythematosus. Rubello Jr. presented a detailed table covering the differential diagnosis of disseminated lupus erythematosus, pemphigus erythematodes, the Brazilian type of pemphigus foliaceus and the European type of pemphigus foliaceus; in his opinion there is much greater difference between disseminated lupus erythematosus and the Senear-Usher syndrome than between Brazilian pemphigus foliaceus and the Senear-Usher syndrome. He was of the opinion that the Brazilian disease could constitute a species of pemphigus foliaceus mid-

way between the European type of pemphigus foliaceus and the Senear-Usher syndrome. He expressed the belief that Brazilian studies will tend to bring the Senear-Usher syndrome into the picture of genuine pemphigus.

Vieria in the following year compared the forme fruste of the Brazilian type of pemphigus foliaceus and the Senear-Usher syndrome. He believed that, although some cases of lupus erythematosus disseminatus have been mistakenly considered as examples of pemphigus erythematosus, true cases of the latter disorder are examples of a forme fruste of pemphigus foliaceus having a strong resemblance to the forme fruste of the South American disease. In conclusion, Vieria recommends that there should be eliminated from inclusion in the Senear-Usher syndrome cases of lupus erythematosus disseminatus, seborrheic dermatitis, parakeratotic eczema and psoriasis, and that only cases of pemphigus of what he regards as a forme fruste of the foliaceus type be included.

It would not be pertinent to detail here the clinical characteristics of the Brazilian type of pemphigus foliaceus, as these can be found in the writings of Vieria and others. But inasmuch as this disorder is generally regarded as an endemic disorder of probably infectious causation, and characterized by observations never seen in pemphigus erythematosus, such as endocrine disorders, ankylosis, osteomalacia, changes of the nails and palmar and plantar keratoderma, we consider that it would be impossible on the basis of present knowledge to determine that the two conditions have in common anything more than some clinical similarities common to pemphigus or pemphigoid diseases.

Another interesting phase of this disorder has been a reversal of the more common situation in which pemphigus erythematosus becomes converted to pemphigus vulgaris or pemphigus foliaceus. Several instances have been recorded in which the clinical picture was originally that of pemphigus of one of the foregoing types but subsequently changed to that of pemphigus erythematosus. As examples of this we may quote Driver, who said: "I think that no one who saw this patient at the start would have suggested a diagnosis of Senear-Usher syndrome. The appearance was more or less typical of pemphigus. A transformation has occurred, and I believe all agree with the diagnosis of Senear-Usher syndrome." Weiss also described a case in which a diagnosis of pemphigus vegetans was verified by about fifteen competent physicians. After a long interval of freedom from eruption, the Senear-Usher syndrome developed; this in turn was followed by generalized exfoliative dermatitis. Becker has reported a similar instance. In some cases such reversal may have resulted when treatment for the pemphigus produced a clinically more benign phase of the disease, although this surely is not the usual course of pemphigus chronicus under treatment. In other instances the reversal has apparently taken place spontaneously.

PROGNOSIS

The first cases of this condition (those seen by Ormsby) and the first one observed by us ran such a prolonged course with little or no interference with the general health that the disorder was considered essentially benign. However, with further experience it became apparent that the reverse was frequently true, and reports began to appear in which there developed a more generalized eruption, assuming the typical form of either pemphigus vulgaris or pemphigus foliaceus, and leading to death. As Ormsby said in 1939, "In going over the literature and studying the matter, I am convinced that in some of these cases a malignant phase develops and death occurs. The patients with early involvement whom we saw did not die, so we viewed the type as benign, but it is not always benign." Wise on several occasions has called attention to the same possibility; likewise, in a number of cases recorded in the literature, subsequent comment has shown that conversion of the picture to that of pemphigus vulgaris or pemphigus foliaceus has led to death. Thus, further experience has led to the removal of one of the early objections to regarding the disorder as pemphigus, namely, its supposedly benign character. In the original article, in which death occurred in only 1 of 11 cases, it was said "that it was possible that further information regarding these cases would disclose a greater proportion of deaths." It can be said, therefore, that in the erythematosus stage the pemphigus is of a relatively benign type and may remain as such for many years. However, when the disease changes to the vulgaris or foliaceus type, the prognosis then becomes that of these types.

HISTOPATHOLOGIC CONSIDERATIONS

With regard to the histopathologic interpretation of cases considered as pemphigus erythematosus there has been, as with the clinical picture, considerable confusion. This we believe can be attributed wholly to one cause, namely, that some cases of disseminated lupus erythematosus with bullae have been mistakenly diagnosed clinically as examples of pemphigus erythematosus.

As Montgomery, who has had the opportunity to study sections from a number of cases, has stated with regard to the microscopic finding in 1 case, "the histologic picture was not that of lupus erythematosus, nor did it present features of pemphigus. The histologic picture of lupus erythematosus is distinctive, whereas, that of pemphigus may be confused with various bullous dermatoses."

Sachs also said that in the bullous type of lupus erythematosus the histologic features of lupus erythematosus are present, while in the case then under consideration no such features were present, and Bloom, who presented the case, remarked that specimens from both the bullae and the crusted types of lesion showed the features of pemphigus and not those of lupus erythematosus.

At a later date Montgomery stated his belief that the histologic picture of pemphigus erythematosus is distinct from that of lupus erythematosus and shows much more inflammatory reaction than that of pemphigus vulgaris. He described the differential observations in greater detail in his discussion of the article of Wile and Arnold.[19] In practically all cases described more recently both here and abroad in which biopsy had been performed, the results were said to be compatible with a diagnosis of pemphigus rather than with one of lupus erythematosus. At present there is such unanimity on this point that in questionable cases we believe the presence of characteristic histopathologic observations of lupus erythematosus should rule out the diagnosis of pemphigus erythematodes.

CONCLUSIONS

From our observations and from an analysis of the literature on pemphigus erythematosus and the Senear-Usher syndrome, we believe that the following conclusions may be drawn:

1. Cases which present the combination of elements suggesting features of lupus erythematosus, seborrheic dermatitis and pemphigus will in most instances prove to be examples of pemphigus erythematodes.

2. The presence of the histopathologic picture of lupus erythematosus should exclude the case from the category of pemphigus erythematosus.

3. In some cases the lupus-erythematosus-like element may predominate, in others the seborrheic and in still others the pemphigoid. With broad experience and with continued observation of individual cases, it is apparent that these varied elements are all part of one basic process. Manifestations closely simulating lupus erythematosus, seborrheic dermatitis and even psoriasis, impetigo and eczema may occur in different cases or at different periods in the same case.

4. Although originally it was thought that pemphigus erythematodes was a benign type, experience has shown that a fatal outcome is not uncommon, once the clinical picture has changed to that of pemphigus vulgaris or pemphigus foliaceus.

5. In exceptional instances pemphigus erythematosus may develop subsequent to, rather than preceding, the vulgaris or foliaceus type of pemphigus.

6. With the acceptance of this disorder as a form of pemphigus and not as an entity, there is no justification for the retention of the designation "Senear-Usher syndrome." The term pemphigus erythematodes, as originally suggested by Ormsby, seems to us to be the most suitable.

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TREATMENT OF EARLY SYPHILIS WITH PENICILLIN G

Administration of Penicillin G in Peanut Oil and Wax Twice Weekly for Eight Weeks

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THE SCHEDULE of treatment discussed in this paper was assigned to Wayne University College of Medicine and the Social Hygiene Clinic of the Detroit Department of Health in March 1946 by the Venereal Disease Committee of the National Research Council, Dr. J. Earle Moore, chairman. Penicillin G in peanut oil and wax (Romansky formula) (600,000 units, 2 cc.) was administered intramuscularly twice weekly for eight weeks. Thus, a total of 9,600,000 units of penicillin was given to the patient in this eight week period. It has been assumed that the most effective results with penicillin in the treatment of syphilis will be secured when a satisfactory level of the drug in the blood is maintained continuously over a given period. The object of this study was to determine whether more widely spaced injections of penicillin continued over a longer period might prove effective in the treatment of a chronic infection such as early syphilis.

Patients with seronegative primary, seropositive primary, secondary or recurrent secondary syphilis were assigned to this treatment schedule. Nearly all the patients were men; 80 per cent were Negro. They were treated between March and November, 1946. A minimum of twenty-four and a maximum of thirty-two months of follow-up is now available in these cases. Table 1 summarizes the number of cases in each classification and the results to date.

A total of 70 patients was treated. Three patients were lost from observation soon after treatment was completed.

Each of the 11 seronegative patients has remained seronegative at the last observation. It has been our experience to secure nearly 100 per cent good results against seronegative primary syphilis with any acceptable method of intensive therapy.

This investigation was carried out with the assistance of funds made available through Wayne University College of Medicine by the Venereal Disease Committee of the National Research Council and the Research Aid Division of the United States Public Health Service.

Of the 20 patients with seropositive primary syphilis, 17 (85 per cent) have progressed to seronegativity and have remained so. One (5 per cent) has remained seropositive at low titer, and 2 (10 per cent) have required retreatment as treatment was a failure.

There are 26 patients with secondary syphilis who have been under observation or have been retreated. Of these, 18 (69 per cent) are clinically and serologically negative; 3 are still seropositive in low titer. Our experience indicates that these last represent serologic fastness and that later serologic or clinical relapse is unlikely. Five of these secondary cases have been classified as treatment failures and retreatment has been undertaken on a basis of seroresistance in fairly high titer, serologic relapse or clinical relapse. Thus, a questionable result was obtained in 11.6 per cent and failure resulted in 19.2 per cent of patients with secondary syphilis.

TABLE 1.—*Summary of Cases of Early Syphilis and Results of Penicillin Therapy*

Classification of Cases		Results	No.	%
Lost from observation	8			
Seronegative primary	11	Negative	11	100.0
Seropositive primary	20	Negative	17	85.0
		Seroresistant	1	5.0
		Failure	2	10.0
Secondary	26	Negative	18	69.2
		Seroresistant	3	11.6
		Failure	5	19.2
Recurrent secondary	10	Negative	10	100.0

Of the 10 patients with recurrent secondary syphilis who are still under observation, all are clinically and serologically negative after two or more years of observation. Recurrent secondary syphilis in our experience has consistently offered a poorer prognosis than secondary syphilis. We have no satisfactory explanation for the excellent results in this series beyond the possibility that many of these cases classified as clinical failures actually represented examples of reinfection. Results for this entire group are shown in table 2.

Seven (10.5 per cent) of the total of 67 patients observed have been classified as therapeutic failures and retreated. Four (5.9 per cent) are still seropositive in low titer, and 56 (83.6 per cent) are clinically and serologically negative. It must be remembered that nearly 50 per cent of these patients had primary syphilis, against which better results can be expected than those for secondary syphilis. In a comparison of results with two different methods of treatment, it is misleading to compare results for the group as a whole unless the proportion of cases in each classification is the same.

Biostatistical analysis of the results of treatment of a disease that is chronic in nature indicates that the simple percentage of failures does not give a true picture of the success or failure. Dr. Margaret Merrill [1] has proposed a statistical method of deriving cumulative failure rates. This method considers the time factor during observation and the fact that cases will be lost before the outcome of treatment is ascertained. It assumes that lost cases will have the same experience of success or failure as those in which patients remain under observation. If Merrill's method of computation is used, the cumulative failure rate of this group after twenty-five to thirty months of observation is 11.3 per cent. Seventy-three per cent of the patients possible to observe were examined at this time. The cumulative failure rate and the percentage of failures in this series correspond closely. This is true because there was a high proportion of the cases held for observation throughout the entire period and there were no additional failures after eighteen months.

TABLE 2.—*Summary of Results of Penicillin Therapy Against Early Syphilis*

	No.	Per Cent
Negative	56	83.6
Seroresistant	4	5.9
Failure	7	10.5

One of the weaknesses of the treatment of early syphilis in the past has been the failure to hold cases until treatment was completed. Conversely, an important advantage of present intensive treatment schedules, particularly under hospitalization, has been the fact that the treatment is completed. It is expected and feared that if a return is made to ambulatory treatment, especially if prolonged over a period of weeks or months, the treatment will again become ineffective through failure to hold these cases. This is especially true of the average clinic patient. It was expected in this group that many of the patients would report for treatment with such irregularity that the schedule would not prove satisfactory. Case holding has, however, been surprisingly good in this series, and our 7 failures and 4 seroresistant cases cannot be blamed on irregularity of treatment. This cooperation might not, however, be secured in future groups because more than average effort was made individually to encourage these patients to continue their treatment on schedule. Table 3 summarizes the regularity of treatment.

Treatment was discontinued in the 2 patients who were receiving penicillin in oil and wax twice weekly because of rather severe urticarial

1. Merrill, M.: Determination of Prognosis Figures in Chronic Disease, Paper no. 238, Department of Biostatistics, School of Hygiene and Public Health, Johns Hopkins University, 1946.

reactions. One patient was transferred to a regimen of aqueous penicillin under hospital supervision and completed his treatment under diphenhydramine hydrochloride (benadryl®) without further difficulty. Treatment of the second patient, who had seronegative primary syphilis, was stopped following the fifth injection (3,000,000 units). Further treatment was not given and the patient has maintained seronegativity to date. Several Detroit physicians have been using this ambulatory schedule in their practice. One relates an interesting experience in which a patient failed to advise the physician immediately as to his reactions. He had a severe urticarial reaction following the sixth injection, a much milder reaction following the seventh, a mild reaction following the eighth and none thereafter. It is our impression that the incidence of allergic reactions is higher on this regimen than with use of penicillin in peanut oil and wax on a daily injection schedule or with aqueous penicillin. This higher incidence could probably be anticipated because of the time between injections and the longer schedule of treatment.

TABLE 3.—*Length of Time Required to Complete Course of Treatment*

No. of Weeks	No. of Cases	Per Cent of Cases
8	40	57.2
9	12	17.2
10	6	6.6
11	4	5.7
12	4	5.7
13	1	1.4
14	1	1.4
15	2	2.8

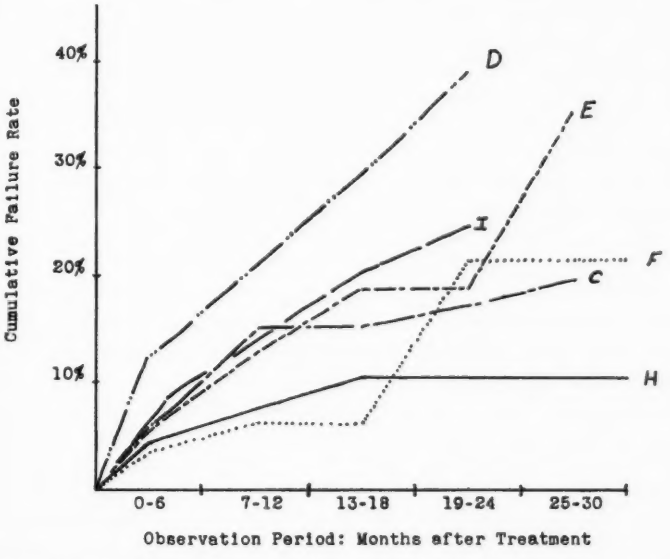
The accompanying chart is a graphic representation of the cumulative failure rates of various schedules of penicillin therapy used at the Detroit Social Hygiene Clinic between 1944 and 1946. Intensive methods of case holding were not used beyond a year, and many cases were lost from observation.

In some instances there is a sharp rise toward the end of the period of observation. This rise seems to occur when there are relatively few of the cases remaining under observation. A few failures (or possible reinfections) at this point have a pronounced influence on the cumulative failure rate. In treatment type F (80,000 units every three hours for one hundred and twenty injections, or 9,600,000 units) the failure rate at eighteen months is 6.1 per cent, while at twenty-four months it is 21.5 per cent. Two failures occurred during the last six month period. However, only 13 cases were still under observation during that time, which accounted for the 15.4 per cent increase in the cumulative failure rate. If all 57 patients treated in this schedule had still been under observation, the failures noted at this time would have increased the cumulative failure rate only 3.5 per cent. It seems, therefore, that no

statistical method of analysis will give satisfactory results unless the majority of cases are observed over a prolonged period.

Treatment method H, which is described in this paper, shows a relatively satisfactory cumulative failure rate compared to the other methods, and no sharp rise in the failure rate. In fact, this comparison shows it to be the most effective of any of the six schedules used. The favorable comparsion is influenced by the better than usual case holding (73 per cent) in this group of patients.

It is our impression that sharp rises in the failure rate late in the period of observation when many cases have been lost from observation



Cumulative failure rates with various schedules of penicillin therapy: treatment methods C, 20,000 units of aqueous penicillin every three hours for 60 injections, 1,200,000 units; D, 20,000 units of aqueous penicillin every three hours for 120 injections, 2,400,000 units; E, 600,000 units of penicillin in oil and wax daily for 8 injections, 4,800,000 units; F, 80,000 units of aqueous penicillin every three hours for 120 injections, 9,600,000 units; H, 600,000 units of penicillin in oil and wax twice a week for eight weeks, 9,600,000 units, and I, 80,000 units of aqueous penicillin every three hours for 60 injections, 4,800,000 units.

do not necessarily indicate a high percentage of late failures from the treatment. Symptomatic treatment failures, patients with reinfections and those who have had a positive serologic test elsewhere will return to the clinic for advice and treatment. Those who consider themselves cured (and may well be cured) do not bother to return. We accept the concept that some apparent relapses may be symptomatic or asympto-

matic reinfections. The only way to keep the statistical analysis reliable is by painstaking case holding and careful evaluation of all cases.

COMMENT

This schedule using penicillin in peanut oil and wax offers an interesting introduction to similar schedules now in use which employ procaine penicillin G in oil.

A larger series (146 patients) has just been completed using the same schedule with procaine penicillin G in oil (600,000 units twice weekly for eight weeks). Like the Romansky formula (penicillin in peanut oil and wax) this preparation maintains satisfactory levels of the drug in the blood for only twenty-four hours. It has the advantage over the latter preparation, however, in that it is more easily administered, much better tolerated locally and causes fewer allergic reactions. It is too soon to attempt a therapeutic appraisal of this second (procaine) series. It is expected that the results will closely parallel those of the series herein reported. Both series represent interrupted levels of penicillin in the blood. By a combination of the results in both series, a larger group of treated patients will be available for comparison in later studies which employ the ninety-six hour repository type of procaine penicillin with absorption-delaying properties.

Micronized penicillin G in oil with 2 per cent aluminum monostearate added as a water repellent is rapidly replacing both penicillin in peanut oil and wax and plain procaine penicillin in oil. This preparation maintains therapeutic blood levels for ninety-six hours after injections of 300,000 units (1 cc.).[2] If given in doses of 600,000 units twice weekly it is indicated that satisfactory blood levels will be continuously maintained. This ninety-six hour type procaine penicillin maintains a continuous but lower level in the blood without the high peak concentration of penicillin in oil and wax or plain procaine penicillin in oil. Good results in the past with arsenic therapy (except for intensive arsenotherapy) have been secured with repeated peak levels of short duration. The question whether better results will be secured with the same total dosage in the same period by interrupted peak dosages or continuous but lower levels needs investigation. It has been assumed that continuous even if lower concentrations such as are secured by ninety-six hour procaine penicllin of the repository type will prove equally effective if not superior. We have begun a third series of cases of early syphilis at the Social Hygiene Clinic of the Detroit Department of Health, using the same schedule but employing the preparation which maintains ninety-six hour concentrations in order to secure data on this point.

2. Thomas, E. W.; Lyons, R. H.; Romansky, M. J.; Rein, C. R., and Kitchen, D. K.: Newer Repository Penicillin Products, J. A. M. A. **137**:1517 (Aug. 21) 1948.

Local tolerance permits large single doses of procaine penicillin. Satisfactory blood cencentrations are reported [2] in excess of five days after single injections of 1,200,000 units of ninety-six hour procaine penicillin in oil. Weekly injections of 1,200,000 units would be more convenient than two injections of 600,000 units. Even if such doses would not maintain therapeutic levels for a full week, our experience with penicillin in peanut oil and wax would indicate that continuous levels are not necessary; it is possible that such single injections might give even superior results. Schedules of this type are now being tried out by ourselves and others.

The problem of minimum effective dosage and duration of treatment requires more investigation. With aqueous penicillin or daily doses of penicillin in oil and wax, 2,400,000 units in eight days seemingly gives as satisfactory results as 4,800,000 units.[3] Thomas [4] believes that the duration of treatment is important and that better results are obtained when the same total dose is given in fifteen days rather than in eight days. Our observations indicate that treatment with 600,000 units of penicillin in oil and wax twice weekly for eight weeks (9,600,000 units) is effective. It is expected that procaine penicillin in oil will prove equally effective. The effect of 600,000 units of the latter given twice weekly for four weeks (4,800,000 units) and for only two weeks (2,400,000 units) must be determined. Further, the results of single weekly injections of 1,200,000 units of procaine penicillin in oil for two, four and eight weeks must be determined. With this information at hand it is possible that more economic schedules permitting better case holding than the eight week schedule herein reported may be employed.

SUMMARY

1. Seventy patients with early syphilis were treated with injections of 600,000 units of penicillin G in peanut oil and wax given twice weekly for eight weeks (total 9,600,000 units). They have now been observed for twenty-four to thirty-two months. Seventy-three per cent are still under observation. The cumulative failure rate has been 11.3 per cent.

2. Of the 70 patients, 75 per cent completed the treatment on schedule or within nine weeks; 95 per cent completed their treatment within twelve weeks, and the remaining 5 per cent completed their treatment within fifteen weeks. Failures were seemingly not related to irregularity in treatment.

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3. Heller, J. R., Jr.; Bowman, R. W., and Price, E. V.: Rapid Treatment of Early Syphilis: Progress Report December 1947, J. Ven. Dis. Inform. **29**:103, 1948.

4. Thomas, E. W.: Recent Developments in the Treatment of Syphilis, Am. J. Pub. Health **38**:1361 (Oct.) 1948.

3. Results would indicate that continuous therapeutic levels of the drug in the blood are not necessary for satisfactory results in the treatment of early syphilis.

4. Ambulatory schedules of this type offer great advantages to both physician and patient. They are particularly adaptable for the newer repository type of procaine penicillin.

5. The question whether the prolonged but lower levels of procaine penicillin in the blood will produce as effective results as the higher interrupted peak levels attained with penicillin in oil and wax remains to be decided.

6. Problems which arise through the recent developments in newer penicillin preparations of the repository type require further investigation.

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VIRUS-PYOGEN SEQUENCE

Interrelationship in Inflammatory Dermatoses: the Clinical Features

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IN A SERIES of scattered papers based on observations covering three decades and intensified in the past ten years, Stokes and his associates have outlined a concept of infection allergy which, when applied to the inflammatory dermatoses as an explanation of onsets, relapse and noncure, they have called the virus-pyogen sensitization sequence. The effort is comparable to the of Milian [1] in outlining the biotropic concept of the activation of infections by drugs with the production of certain types of so-called drug eruptions. To this related field certain observational contributions have been made, particularly in the matter of arsenical exfoliative dermatitis, by Stokes and Cathcart [2] and Stokes and Kulchar.[3] Stokes and Callaway [4] pointed out the types of pyogenic relapse that seemed to follow clinical virus infections, including the epizootic seasonal type, often after a lag, or refractory period, of seven to eleven days, following which the sensitization outburst occurred. Stokes and Beerman have recently reviewed the literature and done some theorizing on the mechanisms

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This article has been abbreviated in the ARCHIVES by omission of some reports of cases; the complete text will appear in the authors' reprints.

1. Milian, G.: Le biotropisme, Paris, Baillière, Tindall & Cox, 1929.

2. Stokes, J. H., and Cathcart, E. P.: Contributory Factors in Post-Arsphenamin Dermatitis, with Special Reference to the Influence of Focal and Intercurrent Infection, Arch. Dermat. & Syph. **7**:14-49 (Jan.) 1923.

3. Stokes, J. H., and Kulchar, G. V.: The Infection-Allergic Complex in Arsphenamine Dermatitic Reaction with Special Reference to Dermatophytosis, Brit. J. Dermat. **46**:134-146 (March) 1934.

4. Stokes, J. H., and Callaway, J. L.: Pyogenic Relapse and Sensitiveness to Light in Certain Dermatoses: Influence of a Factor of Intercurrent Infection, Arch. Dermat. & Syph. **36**:976-983 (Nov.) 1937.

involved, in two papers [5] which it is therefore not necessary to resummarize here. There seems to us good reason to recognize the existence of an infection-activation mechanism in the inflammatory dermatoses, particularly the pyococcic group in which not a drug but another infection, and particularly a virus infection, acts as the activator or sensitizer. In regions in which the virus infections, particularly those of the respiratory and gastrointestinal tract, are common and epizootic or even epidemic, they offer an explanation of the incidence and the up and down or refractory course of a number of the inflammatory dermatoses. They may be complicated by other manifestations of a sensitized state such as photosensitivity, broadening of the base of food-and-contact sensitivity, hypersensitivity to foreign protein (vaccines) and to metals (nickel), and even fatal terminations in conditions such as lupus erythematosus disseminatus, in which a widespread grave, probably vascular, allergy is perhaps the underlying pathologic process.[6]

The purpose of the present paper is to particularize further on the clinical picture of the virus-pyogen sensitivity sequence, largely with the aid of illustrative case reports.

THE CLINICAL PICTURE OF THE VIRUS-PYOGEN SEQUENCE

Our attention was first drawn to the fact that relapse in a group of patients with juvenile or adult acne, with appearance of crops of pustules in an otherwise favorably progressing course, came in chronologic clumps. Over a decade it became apparent that these crops of reactors appeared in successive years at somewhat the same time of year. Two periods were rather clearly identified; the midwinter, or February-March, period and the August-September period. In a patient distribution such as ours, the two seasonal waves among patients east of the Alleghenies can be recognized in any series of carefully taken histories. The August-September wave, sometimes spoken of as "summer flu," has been particularly easy to recognize because of the return of young persons to school with common cold or influenza followed by relapse after three or fourth months of almost complete freedom from lesions. An element of some confusing possibilities is the ragweed season, whose vasomotor rhinitic and also possibly allergic sensitizing influence in predisposing to infection may intermingle with or simulate the August-September epizootic.

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5. Stokes, J. H., and Beerman, H.: Virus Pyogen and Virus Pyogen Photosensitivity Relationships in Cutaneous Disease, Am. J. M. Sc. **213**:494-501 (April) 1947. Stokes, J. H., and Beerman, H.: The Dermatology of Yesterday, To-day and To-morrow, in MacKenna, R. M. B.: Modern Trends in Dermatology, New York, Paul B. Hoeber, Inc., 1948, chap. 1.

6. Stokes, J. H.; Beerman, H., and Ingraham, N. R., Jr.: The "Lupus Erythematosus" Concept: An Attempt at Integration, Am. J. M. Sc. **207**:540-549 (April) 1944.

Our observation of what we now call the pyogen flare in relation to waves of virus infection then led to additional observations as follows:

1. There is a considerable variation in the sensitizing power of different epidemic waves, probably dependent on differences in virus strains or virus type (see subsequent discussion of virus X). There are also differences in persons as to their capacity for sensitization. These range from a species of "virus crippling" in which the susceptibility to virus infection is so extreme and the pyogenic flares so severe and invariable that the patient is virtually incapacitated a large part of the time (cases 13 and 17) to instances in which only an occasional virus infection will, over a period of years, give rise to serious relapse.

2. To sustain a virus-pyogen flare, it is not necessary for the patient to be sensitized by a severe infection. He may have a subclinical infection and flare, or he may have no symptoms of infection while those around him are taken ill. A mother may attend her daughter who has influenza and sore throat and, without becoming ill herself, may experience a sharp exacerbation of her dust-contact and atopic eczema. A teen-age boy may have a violent flare of his acne but no influenza, while other members of his family fall ill around him.

3. The picture of the refractory period as given by Stokes and Callaway (seven to eleven days) is modified by later experience to a range of two to fourteen days from the onset of virus symptoms, probably by the fact that the patient has become a sensitized subclinical carrier before overt symptoms of virus infection appear. A patient may have exceedingly slight symptoms (malaise, nasal discharge for a day, two or three loose stools) and be sharply sensitized, while another with fever and prolonged symptoms of sore throat, respiratory difficulty or diarrhea may escape sensitization entirely, even though flaring occurred on some previous or subsequent occasion.

4. What appear to be symptoms of virus infection (fever, cramps or gastrointestinal symptoms) may intermingle with or be confused with premenstrual flares and may even occur several times, but there is a tendency for the virus-pyogen flare to occur later, after, rather than before, the period.

5. The gastrointestinal symptoms of a significant virus flare-producing infection may range from slight flatulence and constipation, with abdominal cramps for a brief time after the ingestion of food, to a full-fledged attack of acute appendicitis with high fever and enlargement of the mesenteric lymph nodes, with appearance of the characteristic Kaposi-like outbreak a week later as the patient convalesces from the infection plus operation (case 12).

6. It is our impression, not as yet statistically studied, that virus infections with pronounced gastrointestinal symptoms (the so-called virus X infections of 1946-1948, for example) are more sensitizing than those of the upper part of the respiratory tract (coryza without sinusitis).

7. The intermingling of virus with pyogenic manifestations is probably more intimate than a precise chronologic sequence would imply. For example, outbursts of pyogenic lesions of diffuse character and streptococcic and staphylococcic dermatitis may be synchronous with or even preceded by the appearance of herpes simplex or herpes zoster, and the clinical picture of the Kaposi-like varicelliform eruption may be superposed on or take the place of what at other times in the same eczema-asthma–hay fever patient was a simple crop of scattered staphylococcic pustules.

8. A spike or two of high fever from a virus infection at the outset has been seen to improve a staphyloderma, to be followed after the usual week or ten days' refractory period by a pyogenic sensitization flare.

9. Sensitization of pyococci probably indigenous to the skin and succeeding bouts of clinical and subclinical virus infection with their associated pyogenic outbreaks are responsible for a good deal of the up and down course and the winter misery of the atropic or eczema-asthma–hay fever group. In case 18, after a year of freedom from pyogenic outbreaks at the University of New Mexico, a cold contracted by the patient on the train en route East for the Christmas holiday induced a relapse before the patient reached home.

10. One should not be carried away by the virus-pyogen concept to the point of failing to recognize the multiple interacting causes in various types of inflammatory flares; namely, contact and inhalant allergens, emotional crises and photosensitivity. The last mentioned, in particular, we have seen exemplified on several occasions.

11. Since both a clearcut diagnosis of virus infections and an adequate means of prophylaxis and treatment are lacking, a clinical presentation must remain for the time being somewhat shadowy and impressionistic. We have, however, been able to influence the pyogen flare considerably by inducing hyposensitivity to staphylococci with combined vaccine and toxoid therapy using staphylococcus toxoid and bacterial antigen lysed by bacteriophage (ambotoxoid®). Sensitivity to autogenous vaccines has been reported by Norrlind.[7]

7. Norrlind, R.: Prurigo Besnier (Atopic Dermatitis): A Clinical-Experimental Study of Its Pathogenesis with Special Reference to Acute Infections of the Respiratory Tract, Acta dermat.-venereol. (supp. 13) **26**:1-168, 1946.

12. The sensitivity which follows a virus infection tends toward spontaneous remission except in extremely susceptible persons. We have seen evidence of spontaneous regression of the pyogenic flare in as little as one week. An average duration is from several weeks to three months, judged solely by clinical response.

REPORT OF CASES

In the following case histories there are reported a variety of conditions in which the virus-pyogen sequence has been encountered: staphylostreptoderma of the ear in association with otic herpes; various infections of hands and feet; acne vulgaris with photosensitivity; dermatophytic pruritus ani; generalized staphyloderma; psoriasis with staphyloderma, generalized psoriasis; lichen planus with photosensitivity; dermatitis herpetiformis; virus X type of infection with abdominal manifestations, and "virus crippling" with repeated pyogenic episodes.

VIRUS-PYOGEN EPISODES IN STAPHYLOSTREPTODERMA OF THE EAR

CASE 4.—*Diagnostic Summary.*—The virus-pyogen sequence was observed in a patient with staphylogenic and streptogenic dermatitis of the hands and feet. She obtained progressive immunity to virus-pyogen flare after prolonged treatment with staphylococcus toxoid and house dust extract.

History.—K. W., a schoolgirl aged 10 was observed two years for intractable dermatitis of the hands and feet. Her mother had experienced an identical condition twice. The patient had been a feeding problem, with flares on her feet during summers at the shore and on her hands in the fall; the lesions cleared in the winter. Following roentgen therapy there was a general follicular, idlike flare. In March of the first year of observation, the patient had a severe flare when a cold with fever was treated with sulfathiazole sodium (third dose), and a follicular id developed on her trunk. The patient had used a sulfonamide compound locally on a previous occasion without experiencing a bad effect.

An abundant local flora of hemolytic streptococci and staphylococci was identified on culture. Results of patch testing with shoe, glove and other materials were negative. General allergic study revealed decidedly positive responses to glue, stock and autogenous house dust, and some foods. There was a slight local reaction but a decided general reaction to staphylococcus toxoid.

During the second year of observation this child sustained three virus infections with flares of diminishing severity and a fourth without any cutaneous manifestations. The good effect was attributed to simultaneous hyposensitization with house dust extract (autogenous) and staphylococcus toxoid, continued through an entire winter. It was noted in one of the virus-pyogen episodes that erythema-multiforme-like lesions appeared on the hands. There was some question at one time whether the episodes were not accentuated or even produced by the antigenic toxoid, but the large proportion of injections with this agent did not cause any cutaneous exacerbation. Dizziness and epigastric pain had persisted for two days after the last of these toxoid injections, but the symptoms

abated without dermatitic exacerbation on treatment of the patient with castor oil and acetylsalicylic acid. Recovery of the child was reported by the mother.

Hyposensitization to the staphylococcus and to house dust controlled the recurring virus-pyogen flares.

VIRUS EPISODE IN LICHEN PLANUS; PHOTOSENSITIVITY; PENICILLIN SENSITIVITY

CASE 10.—*Diagnostic Summary.*—Typical lichen planus with a virus complication led to sensitivity to light; there was a flare of lichen planus in the light-exposed areas and a flare of previously quiescent dermatophytosis, with possible id; an extension and possible bullous outbreak of the lichen planus occurred; herpes labialis and erythema multiforme (virus type?) developed. Possible sensitivity to penicillin with a threatened exfoliative reaction was observed, with eventual recovery.

History.—G. K., a nervously tense housewife aged 42, presented classic lesions of lichen planus of seven weeks' duration, involving the flexor surfaces of the arms, the thighs, abdomen and soles, with a few typical lesions in the mouth. Roentgen therapy, autohemotherapy and calcium therapy, and the intramuscular injection of bismuth subsalicylate resulted in a gradual though fluctuating improvement in five weeks. A quiescent dermatophytosis of the feet was suspected but not treated. Roentgen radiation was not used on the feet or legs. On May 26 a intertrigo of the groin began to appear. On June 2 the patient sustained a violent attack of diarrhea due to virus X with abdominal cramps. When examined on June 9 she presented: (1) a mouth and lips literally filled with lesions of herpes labialis, (2) a flare of the previously quiescent dermatophytosis interdigitalis; (3) what appeared to be a vesicopustular infection of the id type on the palms; (4) a sharp flare of the lichen planus lesions over the flexor surfaces of the forearms, with a sleeve-delineated margin, and diffuse erythema covering the site of exposure to the sun at Coney Island while she had the menses, and (5) almost complete involution of the lichen planus over the covered portion of the trunk and thighs. From this point the patient was severely ill with the virus infection, and it was feared for a time that a Stevens-Johnson type of erythema multiforme might develop, with profound oral bullous involvement and conjunctivitis. The lichen planus increased in extent; a few bullous lesions were suspected among the extending lesions of lichen planus on the trunk. A crop of deep papules appeared in the palms, suggesting indurated lichen planus of deep shotty vesicles, though fluid was not obtained. On the ninth day of septic fever penicillin therapy was begun; however, it was discontinued in forty-eight hours as signs of urticarial edema and slight exfoliation about the eyelids appeared. The hands and feet manifested an exfoliative reaction, and the lichen planus gradually subsided. When the patient was heard from after discharge, she was steadily improving.

The bismuth may have helped to precipitate both the virus outbreak and the dermatologic flare. An interplay of drug, virus, photosensitivity and antibiotic was present.

VIRUS-PYOGEN SEQUENCE WITH ABDOMINAL MANIFESTATIONS

CASE 12.—*Diagnostic Summary.*—Virus infection of the abdominal type in a pyogen-susceptible child led to, or was accompanied with, appendicitis and terminated in a typical virus-pyogen sequence of pustular lesions, identical with others that had occurred in the past under virus provocation.

History.—E. A. S., a school child aged 9, of allergic parentage, since infancy had been subject to attacks of gastrointestinal and respiratory infection and outbreaks of miliary pustulation in the flexures, over the malar prominences and in the

creases of the neck. The child had no other known allergy and was not sensitive to sulfonamide compounds or penicillin, both of which had been used against repeated attacks of otitis media. The individual outbreaks of flexural staphyloderma resolved under local treatment and diminished gradually in severity. Even a mild cold had an inguinal intertrigo as a sequel in a week or ten days.

In October 1947 the child awakened in the night with violent abdominal pain and rigidity. A diagnosis of probable acute appendicitis was made by the pediatrician and the surgeon. After exploration an appendectomy was performed the next morning. The appendix was inflamed and threatening, but a striking observation was the widespread enlargement and pink color of the mesenteric lymph nodes. The leukocyte count before operation did not exceed 13,000. Convalescence was stormy, with high fever and a consistently low leukocyte count. Knowledge of the child's history led the dermatologist to predict that by the fifth postoperative day an exanthem of the virus-pyogen sequence type would appear in the flexures and over the malar prominences; this is precisely what occurred. The shower of miliary pustules cleared as others had, even without local therapy.

A sibling had had repeated attacks of the Peiffer syndrome in childhood, and the family history is criss-crossed with cutaneous and other manifestations of pyogenic infection "allergy."

THE VIRUS-PYOGEN SEQUENCE IN THE ECZEMA-ASTHMA–HAY FEVER (ATOPIC ECZEMA) COMPLEX

The identification and analysis of the part played by virus-type infections in the eczema-asthma–hay fever complex and the atopic and neurodermatitic pictures is made difficult by the multiple interacting causes in these cases. In our material, concurrent allergy and the intervention of allergens of all types, but especially the seasonal pollens (ragweed particularly) and the contact-inhalant groups represented in house dust, cause confusion by coincidence in time and by exaggerating respiratory symptoms in which infection may also play a part. The person with chronic allergic sinusitis is particularly subject to such puzzling interminglings of symptoms. Another group of persons predisposed to the eczema-asthma–hay fever complex is pyogen susceptible, with pronounced familial and personal histories of pyogenic disturbances. The xerodermic person with this allergic complex also becomes susceptible when his alkali-neutralizing power is reduced by soap. Emotion plays a striking role in the picture of relapse in these patients, and at times the intermingling of emotion and a virus infection (as expressed by a typical herpes and fever with cramps and diarrhea at the height of an emotional storm) is difficult to evaluate. In our case material, the instances in which flares of reaction to a locally injected foreign (staphylococcus) protein occur as coincidences suggest something more than emotion as the activator of the pyogenic response. The influence of emotion on the nasorespiratory and gastrointestinal shock structures being what it is, their lowering of the threshold of virus and pyogenic susceptibility seems a not unreasonable explanatory

concept. Varying with the degree of virus susceptibility and pyogenic susceptibility, we see the clinical picture of virus-pyogen relapse in 1 patient approach the repeated Kaposi varicelliform eruptive type (virus preponderance) while in the person ultrasusceptible to pyogenic responses the relapse after virus infection is, or almost immediately becomes, an impetigo with or without furuncles, a staphylodermic dermatitis or a streptococcic or streptomycotic intertrigo. In the fungus-susceptible person with the eczema-asthma–hay fever complex the virus infection seems to emphasize not so much the mycotic as the pyogenic manifestations of the secondary invader.

The histaminic mechanism can be drawn into the picture either of the virus or the pyogen-susceptible allergic person or of the subject with an eczema-asthma–hay fever complex by the concept of a shift in intestinal flora toward histamine-producing types [8] (violent supraclavicular and facial flush as in case 12).

In the same way, as indicated in Stokes and Callaway's paper and in several of the foregoing cases, a light sensitization mechanism can be conceived to operate through a shift in intestinal flora, following virus infection, toward porphyrin-producing types or at least types associated with the appearance of porphyrins in stool and urine, whether through hepatic injury or otherwise.[4]

Reports of 5 cases are offered as examples of various phases of the virus-pyogen sequence at work among a group of complex causes in the person manifesting eczema-asthma–hay fever susceptibility.

CASE 16.—*Diagnostic Summary.*—An extremely pyogen-susceptible person with allergy of the eczema-asthma–hay fever type exhibited multiple causes of relapse after therapeutic response; these demonstrate the instrumentality and the possibilities for confusion of various aspects of the virus-pyogen sequence.

History.—W. F. M., a business man aged 33, had an allergic family background and had been an inveterate pyogen-susceptible person with pyogenic eczema and furunculosis since infancy, complicated by asthma and hay fever and seldom completely cleared. In addition he was subject to extreme nervous tension in an exacting and vexatious business; his wife was also a victim of allergic ill health. The patient used alcohol in moderation. He was only moderately reactive to staphylococcus toxoid and vaccine. To multiple inhalant allergens, including pollens, wool, feathers and house dust he was violently reactive. He suffered from a self-disclosed Jaquet cutaneous masturbation syndrome with severe excoriation. Simply running hot water over the hands of the patient when he was in a paroxysm of itching would produce an ejaculation.

In the course of four years' observation this patient was largely cleared once but sustained ups and downs associated with all the aforenamed factors operating

8. Kendall, A. I.: Intestinal Intolerance for Carbohydrate, Associated with Overgrowth of the Gas Bacillus (Bacillus Welchii), J. A. M. A. **86**:737-739 (March 13) 1926. Kendall, A. I., and Schmitt, F. O.: Physiologic Action of Certain Cultures of the Gas Bacillus: Studies in Bacterial Metabolism, J. Infect. Dis. **39**:250-259 (Sept.) 1926.

singly or in combination. Some sensitiveness to sunlight was recognized twice. A typical combination of allergic responses is illustrated by flare following a dietary lapse; however, this was preceded by three days of a sneezing episode and fibrositic torticollis. There was coincidental exposure to sunlight while the patient was on a fishing trip. As another example of the sequence, the patient was free of symptoms in July, August and September (even his ragweed-caused hay fever was delayed a month). At the end of September he sustained a simultaneous attack of allergic rhinitis and diarrhea which persisted for several days, with a simultaneous skin flare. The symptoms were relieved almost completely under a regimen of desensitization to house dust and staphylococcus toxoid. The skin remained clear for eighteen months. On one occasion the patient reacted sharply when injections were given while he had a cold (summation of allergens?). The relapse which terminated this free period had the following causes operative in sequence: a visit to the zoo in which he patted sheep (wool allergy); a hunting trip in the latter part of the ragweed season (violent explosion on exposed skin); in December a cold and his wife's influenza led to wholesale extension of the lesions: In addition he was subject at this time to intense pressure from business. A dose of influenza virus vaccine given to the patient during his wife's illness made his condition sharply worse.

A chronic pulmonary or sinus-pulmonary picture began to emerge, and improvement could not be obtained. In June the patient had an attack of "erysipelas" with fever; he reported by phone and disappeared from observation.

COMMENT AND CONCLUSION

The group of case histories summarized herein is a selection from a much larger number drawn from the files because of long duration of the period of observation and the detail of the history. Norrlind helped to validate our anamnestic approach to the virus-pyogen interrelationship in his study of bacterial sensitization in atopic dermatitis, when he found that the overwhelming proportion of the patients who gave self-observed histories of infection flares showed actual bacterial sensitization, while those who did not almost never showed evidence of actual sensitization.

In the frequent use throughout this paper of the word virus there is recognition of the inescapable fact that we, and indeed most investigators of so-called virus disease from the clinical side, have failed to find or have not attempted to demonstrate a virus agent in any part of the picture. We are proceeding on a clinical assumption that certain recurring groups of symptoms are classifiable as those of virus infection, in part because no other agent can be identified. However, the recent literature indicates an increased intensity of search and some positive results in the laboratory in occasional cases. Dingle [9] has called attention to the wide diversity of symptoms for which influenza due to Virus A is now accredited. A recently released statement by the Office

9. Dingle, J. H.: Common Virus Infections of the Respiratory Tract: Diagnosis and Etiology, J. A. M. A. **136**:1084-1088 (April 24) 1948.

of the Surgeon General of the Army credits Kempe [10] with the demonstration "that the virus infection responsible for the respiratory phase of the diseases lumped together as 'virus X' was influenza virus A, the same flu strain responsible for the epidemic of January, 1947, but quite different from the flu virus of 1943 and 1945." The group of often primary atypical pneumonias associated with erythema multiforme and also the so-called eruptive fever with stomatitis, conjunctivitis and balanitis has been searched for causative organisms, Soll [11] finding little or nothing but suspecting a virus, the Commission on Acute Respiratory Diseases discovering nothing,[12] Finland, Jolliffe and Parker [13] observing some evidence of psittacosis-like virus and a herpes virus, but in only 1 of the last groups' 4 patients was a virus actually recovered from the lung. The role of virus infection in the Kaposi varicelliform eruption has been strengthened by recent reports.

It must be frankly conceded, then, that until the appropriate viruses are isolated, reproduce their symptoms of infection in animals and man, and are followed by pyogenic step-up or invasion, we are still dealing with the suggestive and perhaps presumptive, not the demonstrated, relationship.

It will be recalled that we have noted experiences which make it difficult to hypothesize which comes first, the virus or the pyogenic invasion wave or step-up. Much in point on this matter are Lack's [14] observations on the synergism of some gram-positive cocci and vaccinia virus. Lack found a wave of virus proliferation following a coccic invasion, and he attributed it to the spreading factor, hyaluronidase, produced by the staphylococci. The virus is "spread in proportion to the amount of hyaluronidase produced by a concomitant staphylococcal infection and (2) hyaluronidase-producing staphylococci which produce minimal lesions when injected alone, are spread in proportion to their hyaluronidase production when injected with vaccinia virus." If these observations are confirmed, they suggest an interplay by which, through the mediation of hyaluronidase, a staphylococcus spreads virus and a virus acting to stimulate hyaluronidase production by staphylococci

10. Release by the Office of the Surgeon General, Department of the Army, Jan. 26, 1948.

11. Soll, S. N.: Eruptive Fever with Involvement of the Respiratory Tract, Conjunctivitis, Stomatitis and Balanitis, Arch. Int. Med. **79**:475-500 (May) 1947.

12. Association of Pneumonia with Erythema Multiforme Exudativum, Commission on Acute Respiratory Diseases, Arch. Int. Med. **78**:687-710 (Dec.) 1946.

13. Finland, M.; Jolliffe, L. S., and Parker, F., Jr.: Pneumonia and Erythema Multiforme Exudativum, Am. J. Med. **4**:473-492 (April) 1948.

14. Lack, C. H.: On the Synergism of Some Gram-Positive Cocci and Vaccinia Virus, Brit. J. Exper. Path. **29**:191-202 (June) 1948.

spreads staphylococci. However, Lack is careful to say that hyaluronidase is not an exclusive mechanism.

We, like other students of the subject, have called the virus-pyogen sequence an allergic or sensitization affair, realizing that we have named but not explained a mechanism. Scherago's [15] summary well presents the range of phenomena commonly comprehended by such a term. But in saying that a virus infection broadens the base of the allergic state, we have only used another form of words without definition of the mechanism. The sensitization studies of Norrlind and of Storck [16] are approaches to a definition of the phenomenon, but they do not yet define its particular mode of activation.

Therapeutically, the only suggestions to come from this study of virus activation of other infections, and possibly infection-allergic states specifically pyogenic, perhaps dermatophytic and perhaps miscellaneous (psoriasis and dermatitis herpetiformis) are these: A separate use of staphylococcus and bacterial antigen lysed by bacteriophage toxoid (ambotoxoid®), or its combined use with an autogenous house dust extract for hyposensitization purposes showed some signs of reducing the susceptibility of some patients to their virus-pyogen flares. A few attempts to hyposensitize with a stock cold vaccine and with autogenous staphylococcus vaccine did not seem promising. Climatic escape did not result in a rapid desensitization of the patient from his pyogenic susceptibility, and recurrence followed rather promptly on reexposure to virus.

Attention to the other elements of a complex background including other allergens, emotional stress, exhaustion and focal infection remains as important as ever.

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15. Scherago, M.: Bacterial Allergy, Ann. Allergy **5**:1-18 (Jan.-Feb.) 1947.

16. Storck, H.: Experimentelle Untersuchungen zur Frage der Bedeutung von Mikroben in der Ekzemgenese, Dermatologica **96**:177-262, 1948.

GASSING OF FUNGI

A Preliminary Report

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THE USE of gas to kill fungi on the skin or scalp has to our knowledge never been tried. Gases have been employed to kill bacteria and fungi in fumigating processes in homes and ships and in horticulture. In the field of medicine, formaldehyde has been used to destroy myceliums and spores in shoes to prevent reinfection. However, the excessively long time of exposure required by this gas plus its irritant action made its use impractical for our purpose. The difficulty has been to obtain a relatively harmless gas—that is, one safe to handle, nonlethal to workers and patients and nonirritating to the skin. Second, the gas must act in a short enough time to be practical and to kill both the myceliums and spores. It was our plan to study various gases to determine whether one could be found which would fulfil our requirements.

MATERIAL AND METHODS

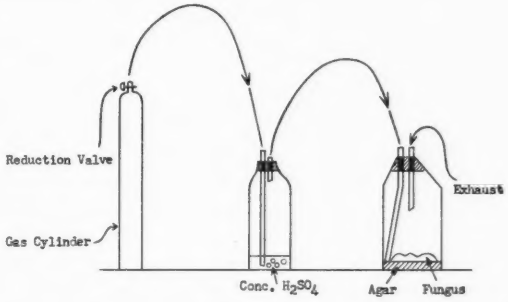
The first step was to set up the necessary laboratory apparatus and to establish criteria which would ascertain the fungicidal action of the gases tested. It was decided to use subculturing as the basis for determining the fungicidal effectiveness of the gases and also to observe these subcultures for growth for at least two weeks, as was established by Emmons,[1] before a final negative reading was made.

For our experiments we used four of the commoner fungi cultured from patients with tinea capitis and dermatophytosis: Microsporon audouini, Microsporon lanosum, Trichophyton purpureum and Trichophyton gypseum. The fungi were planted on Sabouraud's dextrose agar medium in 300 cc. Erlenmeyer flasks, which were stoppered with cotton plugs. The cultures were planted with a flamed loop, and the precaution of flaming the mouths of the flasks was also taken to lower the incidence of contamination. Only cultures without contaminants were used in our experiments. The cultures were allowed to grow out for

1. Emmons, C. W.: Fungicidal Action of Some Common Disinfectants on Two Dermatophytes, Arch. Dermat. & Syph. **28**:15 (July) 1933.

a period of two weeks and to attain a luxuriant growth before they were exposed to any gas. The apparatus used in our experiments is represented diagrammatically in the accompanying figure.

The cultures were exposed to several gases for periods ranging from thirty minutes to two hours. This was done by slowly running the gas into the bottom of the flask and displacing the air in the flask upward. After exposure for the period mentioned, the exposed cultures were subcultured and planted directly on fresh Sabouraud's dextrose agar, again taking the necessary precautions to avoid contamination. The subcultures were examined weekly over the period of one month, and the original cultures which had been exposed to the gas were also kept under observation for the same time.



Chlorine gas is considerably heavier than air, and by introducing it slowly into the bottom of the flask (40 bubbles per minute) the air in the flask was displaced upward. The sulfuric acid bath is for the purpose of further dehydrating the gas.

For our experiments, three easily obtainable gases were chosen: nitrous oxide, chlorine and carbon monoxide. Each of these gases was run through the series of steps previously described. Carbon monoxide proved exceedingly difficult to handle and was dropped from the series. It certainly would have proved too dangerous for use on a large scale. Next, the complete series of steps was run through with nitrous oxide without any remarkable results. Exposures up to twelve hours were attempted with this agent, and still there was no evidence of fungicidal action. Last, the same procedures were repeated with chlorine (anhydrous). The best results by far in our in vitro experiments were obtained with this gas. We repeated the tests several times with chlorine for the exposure times designated, and uniformly excellent results were obtained. To date there has been no evidence of growth in cultures of any of the four fungi after thirty minutes' exposure to chlorine.

Chlorine is easily handled and controlled. Its pungent odor is characteristic, and its yellow-green color is readily recognized. The gas

is considerably heavier than air, having an atomic weight of 35.4 and a specific gravity of 2.45. It has been used for many years to bleach cotton and other forms of cellulose and for sterilization. Originally it was employed in the form of chloride of lime, or bleaching powder. Subsequently it was used as Labarraque's solution, or Javelle solution, which was prepared from chloride of lime by admixture with suitable quantities of alkalis, such as sodium carbonate and sodium bicarbonate, and water; the resultant clear liquor was used. During World War I chlorine was extensively used in surgical work in the form of diluted sodium hypochlorite solution (modified Dakin's solution). This was a modified and carefully prepared Labarraque's solution with a concentration of about 0.45 per cent sodium hypochlorite. In more recent years chlorine has been available as a pure gas compressed in cylinders, and as such has largely replaced chloride of lime.

The chemical activity of chlorine in any form used for bleaching or sterilization depends on the exposure of the material to be treated to hypochlorite, which in decomposing to the chloride gives up nascent oxygen:

$$Cl_2 + H_2O \longrightarrow HOCl + HCl$$
$$2\ HOCl \longrightarrow O_2 + 2\ HCl$$

(or as in diluted sodium hypochlorite solution)

$$2\ NaOCl \longrightarrow 2\ NaCl + O_2$$

Those who work in plants where bleaching powder and chlorine are manufactured seem to tolerate the gas in high concentrations over long periods of time. Diluted sodium hypochlorite solution was used with good results in open infected wounds, where it dissolved and destroyed necrotic tissue and stimulated the formation of healthy granulation tissue. Exposure of healthy skin, moist or dry, to chlorine does not seem to result in deleterious effects. In testing the gas on our own skin, both moist and dry, only a slight erythema resulted after thirty minutes' exposure to high concentrations.

In 1931 Schamberg, Brown and Harkins [2] demonstrated that iodine in 1:85 dilution killed Epidermophyton inguinale after exposure for thirteen minutes. Iodine solutions are being used today as fungicides with some good results, especially against dermatophytosis. Iodine gas is much too toxic and irritating to be used in our experiments. It is mentioned solely because it is a member of the halogen family along with chlorine. Attempts were made at this time to increase the activity of iodine by photosynthesis, but the desired effects were not obtained.

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2. Schamberg, J. F.; Brown, H., and Harkins, M. J.: Chemotherapy of Ringworm Infection: Preliminary Report, Arch. Dermat. & Syph. **24**:1033 (Dec.) 1931.

Emmons [3] in 1933 compared the fungicidal action of many agents with phenol and at this time assigned iodine a phenol coefficient of 3,000 against T. gypseum and Monilia albicans. However, a phenol coefficient was not determined or assigned to chlorine during these studies. Still earlier, in 1922, Schamberg and Kolmer [4] determined that mercuric chloride was effective as a fungicide. Nowhere in their report was there any mention of the effectiveness of chlorine. Of the substances studied, iodine and chlorine (diluted sodium hypochlorite solution) had the highest phenol coefficient by the method used.

Bograd [5] in 1943 reported the use of ethyl chloride as a fungicide with excellent results. He was unable to find any contraindications to its use, even though in many of the cases reported the lesions became secondarily infected. It was his opinion that fungicides in ointment bases definitely retard healing during treatment with ethyl chloride. Whether this is also true with regard to chlorine will have to be determined.

However, chlorine is not the only gas which is effective as a fungicide. Hydrogen cyanide, as reported by Polunin,[6] is effective in killing both colonies and spores of fungi. However, this gas is rapidly changed into harmless combinations with the aid of sulfur supplied by compounds of albumin and may, therefore, have little or no effect against fungi when used on human skin. Fungi also have a high content of sulfur, which would function in a similar manner and thereby make them more resistant to hydrogen cyanide.

It is our belief that chlorine can be used effectively in the treatment of fungous infections of the glabrous skin and scalp. Due to its physical characteristics, the gas can be readily controlled. The skin will supply the water necessary for the desired chemical reaction, and, as has been shown, this reaction is relatively nonirritating to the skin. Chlorine is not suitable for bleaching animal hair for use in textiles because it causes the hair to become brittle and break easily. The effect of chlorine on human hair has not been determined as yet, but in treating the scalp it would be desirable to have the scalp clipped or shaved as for roentgenologic epilation. To date ointments and solutions used in the treatment of tinea capitis have been relatively ineffective without

3. Emmons, C. W.: Fungicidal Action of Some Common Disinfectants on Two Dermatophytes, Arch. Dermat. & Syph. **28**:15 (July) 1933.

4. Schamberg, J. F., and Kolmer, J. A.: Studies in the Chemotherapy of Fungus Infections: I. The Fungistatic and Fungicidal Activity of Various Dyes and Medicaments, Arch. Dermat. & Syph. **6**:746 (Dec.) 1922.

5. Bograd, N.: Treatment of Tinea with Ethyl Chloride, Arch. Dermat. & Syph. **48**:511 (Nov.) 1943.

6. Polunin, N.: High Concentration Hydrogen Cyanide Fumigation of Fungi and Bacteria, Nature, London **150**:682 (Dec. 12) 1942.

previous epilation of the scalp, because the spores present on the hair shaft within the scalp are not reached by the medicament. It is our belief that chlorine can penetrate this barrier and act on the spores there. This procedure will be investigated by us as a continuation of this study, as will the effect of chlorine on determatophytosis of the hands and feet.

SUMMARY

Four common fungi (M. audouini, M. lanosum, T. purpureum and T. gypseum) were exposed in vitro to chlorine. After thirty minutes' exposure to this gas it was concluded that the myceliums and spores had been destroyed, inasmuch as the originally gassed cultures and subcultures taken from them showed no signs of life after an observation period of four weeks. Chlorine is easily controlled and is relatively non-irritating to the skin. Further studies will determine the exact minimum exposure time necessary for in vivo effectiveness against fungi and also whether follow-up or additional treatments will be required.

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EPITHELIOMA

Clinical and Histologic Data on 1,025 Lesions

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WHILE the specific etiology of cancer continues to elude detection by any means of investigation known to medical science, epithelium continues to provide both researcher and clinician with an easily available site for studying the behavior of this pathologic mystery. The importance of the skin as a site of primary cancer has been recognized apparently since ancient times. According to Oberling, "The first primitive notions on what was later to be named cancer must have come from watching *ulcerations of the skin* that were refractory to all treatment, for an account of these in an Egyptian papyrus of the fifteenth century B. C. constitutes one of the earliest known references to the disease." [1]

Many of our patients, including some of very little formal education, recognize epitheliomas on their own persons and present themselves more or less resigned to what they fear is a serious fate. Fortunately, they come in earlier than such patients did years ago, and, with proper treatment, cure is now assured in well over 90 per cent of the cases (with the possible exception of lesions of the mucous membrane).

For some years, two of us (J. A. E. and D. G. W.) have studied the subject of epithelioma with more than ordinary interest. Since 1939 we have kept a detailed clinical registry of all the patients with epithelioma whom we have seen. In 1944 we reported an analysis of the clinical observations made while we treated 1,742 patients with a total of 1,928 epitheliomas. In that report we discussed etiology, the type of skin and the role of pigment, the carcinogenic effect of ultraviolet rays, the prevalence of cutaneous cancer in different areas of the United States and climatologic data. Of the 1,052 patients we were able to follow for five years or longer, 97.1 per cent gave every evidence of having been cured. We concluded that "the high incidence of

1. Oberling, C.: The Riddle of Cancer, translated by W. H. Woglom, New Haven, Yale University Press, 1944, pp. 10-15.

epithelioma in the white population of the Southern States supports the concept of an etiologic relationship between solar radiation and skin cancer and emphasizes the importance of the therapeutic problem."[2]

We present herewith certain clinical data on 1,257 additional patients seen from July 1941 through December 1947 with particular attention directed to the histologic observations of 1,025 specimens. Dr. Kimmelstiel has contributed the histopathologic classification and discussion. Since many of these patients have been followed for less than five years, we are not including a tabulation of results in this group. It is our intention to supply this tabulation at a later date. So far as we can tell at this time, our percentage of cures has not decreased.

CLINICAL DATA

In general, the clinical observations made on this group of patients are similar to those published in our previous report, with the exception of those concerning the size of the lesions (table 6). In those tables which include a cross tabulation of one or more clinical findings against the microscopic type of the lesion, we have used the diagnostic terminology employed at the time the specimen was first examined. Because Foot's classification of adnexal tumors[3] was not applied to our material until after January 1947, our individual microscopic diagnoses prior to that date were of the generally used standard categories. All the 1,025 microscopic specimens, however, have been reviewed and reclassified by Kimmelstiel; his discussion follows the presentation of our clinical data.

TABLE 1.—*Age of 1,257 Patients, by Decades*

Decade	Number of Patients	Percentage of Total Number	Percentage Appearing in Previous Report (1,754 Patients)
10-19	5	0.4	0.1
20-29	25	1.9	1.9
30-39	108	8.5	6.9
40-49	236	18.7	15.7
50-59	305	24.2	27.7
60-69	330	26.2	25.3
70-79	205	16.5	18.4
80-89	43	3.4	3.5
90 +	0	...	...

Age.—The age distribution by decades is shown in table 1. The greatest number of cases, 26.2 per cent of the total, occurred in the

2. Elliott, J. A., and Welton, D. G.: Epithelioma: Report on 1,742 Treated Patients, Arch. Dermat. & Syph. **53**:307 (April) 1946.

3. Foot, N. C.: Adnexal Carcinoma of the Skin, Am. J. Path. **23**:1 (Jan.) 1947.

group of patients aged 60 to 69; the next greatest number, 24.2 per cent of the total, were observed in persons in the sixth decade. It is clear that the frequency of cutaneous cancer increases with each decade up through the seventh decade; after age 70 there is a relative decline in its occurrence, which observation is explained in great part by the fact that only a small percentage of the population lives beyond 70 years.

Sex.—Of this group of 1,257 patients, 56.4 per cent were men; this figure is 1 per cent less than that reported for men in our previous paper (table 2), in spite of the fact that our present data include reports on lesions of the mucous membrane. An analysis of the distribution by sex in the three standard microscopic categories is shown in table 3.

TABLE 2.—*Distribution by Sex of 1,257 Patients*

Sex	Number	Percentage	Percentage in Previous Report (1,742 Patients)
Male	710	56.4	57.4
Female	547	43.6	42.6

TABLE 3.—*Distribution by Sex and Microscopic Type of 1,025 Epitheliomas*

	Cell Type							
	Basal		Squamous		Basal-Squamous			
Sex	Number	Percentage	Number	Percentage	Number	Percentage	Total	Percentage of Total
Male	333	53.7	234	67.2	29	50.8	596	58.1
Female	287	46.3	114	32.8	28	49.2	429	41.9
Total	620	100.0	348	100.0	57	100.0	1,025	100.0

We found that the male patients had (1) more than twice as many squamous cell lesions as did the female ones, (2) a majority of the basal cell lesions and (3) virtually the same number of basal-squamous cell lesions as was found in the female patients. The only significant sex differential appears in the squamous cell category. Although the inclusion of lesions of the mucous membrane in this study undoubtedly contributes to this finding (lesions of the lower lip—see table 7), that fact alone is insufficient to account for the entire difference. Our findings here are in agreement with those in other reports in the literature which indicate that men are much more susceptible to squamous cell lesions than are women.

Occupation.—In this study we endeavored to ascertain whether or not the occupational environment of each patient was over 50 per cent outdoors; the results are shown in table 4. If one subscribes to the theory that excessive solar radiation is a significant etiologic factor in

epithelioma, the results here appear at first to be disappointing. At least two interfering factors are to be considered, however. First, it is difficult, if not impossible, to obtain an accurate estimate of this item from the average patient. Second, many of those who are by occupation indoors more than 50 per cent of the time spend an equal or greater amount of time outdoors in various avocations or sustain severe overexposure to sunlight frequently or periodically.

Duration.—We still find this factor difficult to ascertain accurately. Although a lesion on the face is usually noticed early by the patient or one of his family, memory of that notation is rarely fixed at a specific date. Consequently, a general impression is the best obtainable estimate in most cases. Our findings, shown in table 5, are very similar to those reported previously, with the largest number of patients (46.3

TABLE 4.—*Occupational Environment of 1,257 Patients*

	Number of Patients	Percentage	Percentage in Previous Report (1,742 Patients)
Indoor	726	57.5	59.4
Outdoor	535	42.5	40.6

TABLE 5.—*Duration of Epitheliomas in 1,257 Patients*

	Months		Years				
Period *	1-3	4-12	1-3	4-6	7-10	11-20	20+
Number	167	252	582	132	59	47	18
Percentage of total	13.2	20.0	46.3	10.5	4.7	3.7	1.4
Percentage in previous report	14.8	21.6	38.6	13.1	5.8	4.5	1.2

* Period indicates the time between the date the patient recalled having first noticed the lesion and the day he reported for treatment.

per cent) waiting from one to three years after noticing a lesion before seeking treatment. The frequency increases up to this period of time and decreases uniformly over the longer duration periods. With the great amount of cancer education "beamed" at the lay public these days, one may justifiably expect to see the percentage increase in the less than twelve months groups in another five years or so.

Size of Lesions.—The lesions were divided into four groups, according to their surface diameter: small (less than 0.5 cm.), medium (0.5 to 1.0 cm.), large (1.0 to 5.0 cm.), and giant (over 5.0 cm.). This classification is, at best, only a rough indication, since many epitheliomas are more extensive than their surface appearance indicates. Table 6 shows that only 13.5 per cent of all lesions were small, this figure being in decided contrast to that of 45.6 per cent for small lesions in our previous report; the difference may be due to the stressing of

more accurate measurement during the present study. The medium-sized lesions accounted for 38.8 per cent, while the greatest number—46.8 per cent—was of the large lesions; this observation contrasts strikingly with a finding of 27.9 per cent for this size range in our previous study. A few lesions of more than 5.0 cm. in surface diameter were classified as giant.

Table 6 also reveals the distribution by size among the three standard microscopic types. We find that 72 per cent of the small lesions, 62 per cent of those of medium size and 56 per cent of the large lesions were of the basal cell type. Thus it is suggested that, the larger the size of the lesions, the higher is the percentage of the squamous cell type.

Location.—That most epitheliomas occur on the exposed portions of the skin is generally recognized. In our present study 87.9 per cent of all the lesions occurred on the face and neck; the tabulation for each site is found in table 7. As in our previous report, the cheek and the

TABLE 6.—*Size and Microscopic Type of 1,025 Epitheliomas*

Size	Small					Medium					Large					Giant			
Microscopic Type*	B	S	B-S	Total	% of Total	B	S	B-S	Total	% of Total	B	S	B-S	Total	% of Total	B	S	Total	% of Total
No. of lesions	100	32	7	139	13.5	247	127	24	398	38.8	269	185	26	480	46.8	4	4	8	0.7
Percentage of type.....	72	23	5	...	....	62	32	6	...	....	56	38	5	...	....	50	50	..	...
Percentage of total in previous report..					45.6	...	...	..	...	26.4					27.9				

* Indicates basal cell tumors; S, squamous cell tumors, and B-S, basal-squamous cell tumors.

nose lead as individual sites, accounting for 47.7 per cent of all the lesions. These observations represent, in our opinion, important clinical evidence supporting the concept of solar radiation as a significant etiologic agent.

Table 7 also presents a detailed tabulation of distribution of lesions according to microscopic type and sex. Male patients presented the majority of all the lesions (58.1 per cent) and led numerically in each microscopic type except the basal-squamous cell variety, the occurrence of which was evenly divided numerically (on a percentage basis, the incidence was actually higher in the women). Other significant observations illustrated in this table include the following points: (1) All lesions of the lower lip were in men; the one lesion of the mucous membrane of the upper lip, however, was in a woman; (2) male patients presented over two thirds of the lesions occurring on the ear, jaw and hand; (3) women had more than two thirds of the epitheliomas found on the forehead, nasolabial area, chin, arm and leg, and also 60 per cent of the lesions of the tongue; (4) lesions of the hand and of the lower lip were predominantly squamous cell in both

sexes, but those of the ear were of this type only in men; (5) the distribution by location of the basal-squamous cell lesions was approximately parallel to that of the basal cell lesions (this observation provides

TABLE 7.—*Location and Microscopic Type* of Lesions*

Location (In Order of Incidence)	Male Patients					Female Patients					Grand Total	% of Total No.
	B	S	B-S	Total	% of Both Sexes	B	S	B-S	Total	% of Both Sexes		
Cheek	97	50	9	156	61.1	64	34	1	99	38.9	255	24.8
Nose	97	20	7	124	52.7	79	23	9	111	47.3	235	22.9
Neck	17	19	1	37	56.0	20	4	5	29	44.0	66	6.4
Mucous membrane of lower lip	2	63	..	65	100.0	..	..	..	..	....	65	6.3
Temple	21	12	4	37	58.7	20	5	1	26	41.3	63	6.1
Ear	17	23	2	42	77.7	8	3	1	12	22.3	54	5.2
Nasolabial area (skin of upper lip)	16	1	..	17	33.3	28	5	1	34	66.6	51	4.9
Forehead	10	6	..	16	32.0	24	9	1	34	68.0	50	4.8
Body	14	3	..	17	48.5	8	7	3	18	51.5	35	3.4
Hand	2	19	1	22	66.6	2	8	1	11	33.3	33	3.2
Jaw	11	4	3	18	69.2	4	3	1	8	30.8	26	2.5
Eyelid (skin)	17	2	..	19	76.0	5	1	..	6	24.0	25	2.4
Scalp	5	3	1	9	52.9	8	..	..	8	47.1	17	1.6
Chin	3	2	..	5	29.4	9	1	2	12	70.6	17	1.6
Arm	1	1	1	3	27.2	5	3	..	8	72.8	11	1.0
Finger	2	2	..	4	50.0	3	..	1	4	50.0	8	0.7
Leg	1	..	..	1	20.0	..	3	1	4	80.0	5	0.4
Tongue	..	2	..	2	40.0	..	3	..	3	60.0	5	0.4
Buccal mucous membrane	..	1	..	1	50.0	..	1	..	1	50.0	2	0.1
Penis	..	1	..	1	100.0	..	..	..	..	....	1	...
Mucous membrane of upper lip	..	..	..	..	....	..	1	..	1	100.0	1	...
Totals	333	234	29	596	58.1	287	114	28	429	41.9	1,025	100.0

* Microscopic type is indicated as follows: basal cell epithelioma by B; squamous cell, S, and basal-squamous cell, B-S.

TABLE 8.—*Type of Skin and Microscopic Type of Lesion for 1,025 Epitheliomas**

Type of Skin	Male Patients					Female Patients					Grand Total	% of Total
	Number of Lesions				% of Group	Number of Lesions				% of Group		
	B	S	B-S	Total		B	S	B-S	Total			
Blond	288	203	21	512	85.7	235	106	22	363	84.6	875	84.4
Brunet	45	31	8	84	14.3	52	8	6	66	15.4	150	14.6

* Microscopic type is indicated as follows: basal cell epithelioma by B; squamous cell, S; and basal-squamous cell, B-S.

an interesting correlation with the histologic classification discussed later in the paper). Sutton presented a similar cross tabulation in his analysis of 560 basal cell carcinomas.[4]

4. Sutton, R. L., Jr.: Carcinoma of the Skin, J. Missouri M. A. **39**:203 (July) 1943.

Type of Skin.—Another axiom in the lore of cutaneous cancer is that epitheliomas occur much more commonly in blond persons than in brunets. While experimental and theoretic considerations cited in our previous report strengthened this general impression, we did not at that time have definite clinical data on this point. In our present study we have tabulated data on this factor and found that 84.4 per cent of all the lesions occurred in blonds. Table 8 shows this tabulation, also broken down according to microscopic type. This information, again, is confirmatory evidence supporting the concept of solar radiation and susceptible skin type in the pathogenesis of epitheliomas.

HISTOPATHOLOGY

This histologic analysis is based on a study of 968 specimens [5] previously diagnosed as either squamous cell, basal cell, or basal-squamous cell epitheliomas. A large number of these tumors have been shifted vacillatingly from one group into another, and this review was undertaken with an attempt to arrive at a clearer understanding and integration of the various types.

A survey of textbooks and current literature leaves the impression that little doubt exists concerning the origin of so-called basal cell tumors from the basal layer of the epidermis or corresponding layer of hair shafts.

In a recent article, however, Foot [3] has given new impetus to Mallory's theory of the "hair matrix carcinoma." He has modified this concept by postulating that these tumors derive from adnexal primordia and accordingly proposed a new terminology and classification. He suggested the term "adnexal carcinoma." The justification for this terminology lies largely in the fact that a great number of so-called basal cell tumors show evidence of varying degrees of differentiation, simulating more or less abortive hair follicles, sebaceous glands and sweat glands.

In accordance with the accepted principles of oncologic terminology the term basal cell tumor implies that the cells of the tumor maintain the character of basal cells. This situation, in our own experience, exists for no more than half the cases. The occurrence of squamous epithelial cells, with or without more or less well developed horny pearls, in the center of nests of otherwise typical basal cell epitheliomas is so frequent, the degree of specificity of differentiation so variable and the transition so insidious that inextricable confusion results if one attempts to separate such tumors into distinct entities, such as basal

5. Fifty-seven specimens are not included because the amount of tissue was inadequate to justify a microscopic diagnosis of epithelioma; all these specimens, however, were from clinically epitheliomatous lesions and were therefore included in our clinical tabulations.

cell and basal-squamous cell epitheliomas. Likewise, in a considerable number of so-called basal cell tumors, tubular-like structures develop in varying degrees of specificity and numbers, making the distinction between basal cell and sudoriparous, hidradenomatous tumors a matter of arbitrary decision.

It appeared to us, therefore, that Foot's concept of "adnexal tumor" assists in the understanding of these numerous transitional structures, and we have adopted his classification as a basis for our analysis. We attempted in particular to determine how much evidence of differentiation in one or the other direction could be found in so-called basal cell epitheliomas. The bulk of the material could be readily fitted into Foot's pattern, but certain exceptions were noted which we believe to be significant and which will be discussed in some detail.

The material submitted for histologic study was obtained by curettage. In the vast majority of cases the bulk of the tumor and its relationship to the overlying epidermis could be analyzed adequately. Five per cent of the specimens had to be discarded as unsatisfactory. This method of biopsy of the skin does not permit a survey of the entire mass. Variations in the structural pattern of the growth may thus have been missed. The resulting inadequacy of accurate classification, however, is believed to have been overcome because of the large number of cases examined and, furthermore, as we concluded, appears to be of little significance.

The following table of classification, which is not claimed to approach accuracy, is presented for the purpose of guiding the comment:

			Number of Cases	Percentage of Total
I.	Squamous cell epithelioma		293	30.2
II.	Acanthoma, bordering malignancy		33	3.4
III.	Adnexal carcinoma		555	57.2
	A. Pilar type			
	1. Pilar type proper	103		
	2. Primordial type	286		
	3. Ribbon type	54		
	4. Cystic type	13		
	5. Unclassified	45		
	B. Sudoriparous, glandular type	23		
	C. Pilar or sudoriparous type	31		
IV.	"Basal celled" type		20	2.1
V.	Transitional		67	6.9

CLASSIFICATION OF TUMORS

I. *Squamous Cell Epithelioma.*—We were surprised at the large number of cases in which we were unable to come to a satisfactory conclusion as to whether an acanthotic penetrating epidermis should be called benign or malignant. These cases included seborrheic warts and constituted 11.3 per cent of the squamous cell epitheliomas. Detailed description is not indicated. It suffices to say that we ourselves have

fluctuated in our diagnoses, from one of low grade malignant growth to that of benign growth, on reexamination of these sections. Failure to arrive at a definitive conclusion in such a high percentage of cases is not reflected in many other reports, a circumstance for which no satis-

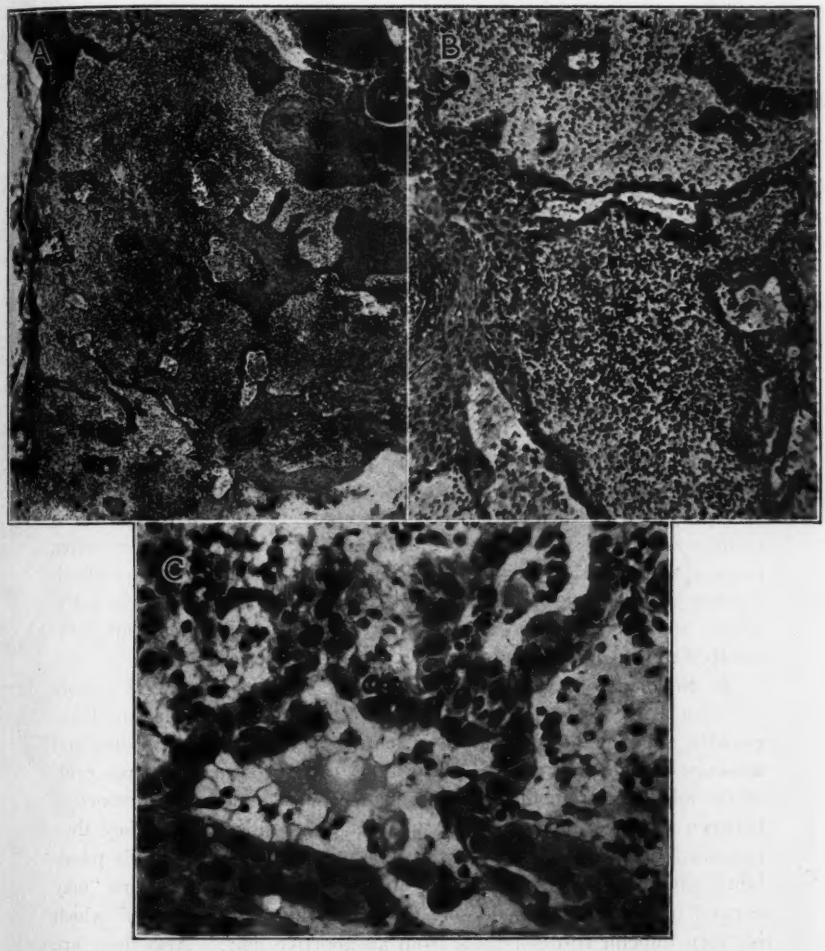

Fig. 1.—Transitional type. (Different magnifications of the same tumor.) *A*, low power view, showing a stratified squamous cell epithelioma infiltrating and forming atypical hair follicles, from which glandular structures originate. *B*, medium power view, in which a portion of an atypical hair follicle with tubules in direct continuity with its basal layer may be seen. *C*, high power view, showing sudoriparous structures, partially lined by a double layer of cuboidal cells.

factory explanation appears. The high percentage of cures of epitheliomas of the skin makes it impossible for us to reevaluate our diagnosis by follow-up of these cases.

II. *Adnexal Carcinomas.*—A. Pilar Type: Typical examples of all of the subgroups, according to Foot's descriptions and illustrations, could readily be found in relatively large numbers; but the figures given in the tables are far from being accurate, since numerous cases were encountered in which the subgroups were combined in various proportions. The degree of differentiation of the "primordial" type into the pilar type proper or ribbon type varies, not only from case to case, but also within various portions of a single section. There is, however, no question that the primordial feature is the commonest one. We also agree with Foot that whorl formation and keratinization in the center of tumor cell nests are rather common, being characteristic for 22 per cent of all tumors of the pilar type. The percentage would have been even higher if we had been strictly consistent and included in this group all cases in which there were isolated or incompletely developed foci of central lamination and formation of squamous-like cells. According to description and definition, many of these tumors would appear in other statistics under the term of basal-squamous cell epithelioma.

It is questionable to us whether or not the cystic type can be recognized as a separate subdivision. The pilar and the ribbon type seem to represent a distinct pattern of differentiation; most of the instances of the cystic type, however, were apparently a result of a degenerative process, the details of which are well known and need not be redescribed. Twenty cases of unclassified adnexal tumors are included in which the biopsy specimen was too small for proper subclassification, but sufficiently large to identify nests of the primordial type.

B. Sudoriparous Glandular Type: We have found only 23 tumors for which we are reasonably certain of accurate classification, these growths showing the characteristic features as described by Gates and associates,[6] Foot and others. Thirty-one, or approximately 6 per cent, of the adnexal carcinomas showed features which made the distinction between the pilar and the sudoriparous type difficult, and they thus remained open to subjective interpretation. Foot admitted this possibility when he stated that lumens in such sudoriparous tumors "may expand into a small cyst, loosely filled with keratinized scales," which is "then difficult to distinguish from an abortive hair." Also there are many cases in which in a primordial type of adnexal tumor there develop cystlike spaces lined by a single or double layer of cuboidal

6. Gates, O.; Warren, S., and Warvi, W. N.: Tumors of Sweat Glands, Am. J. Path. **19**:591 (July) 1943.

cells and resembling imperfect ducts or tubules. We could not be certain in every instance whether these spaces resulted from degeneration or were manifestations of potential differentiation. In these

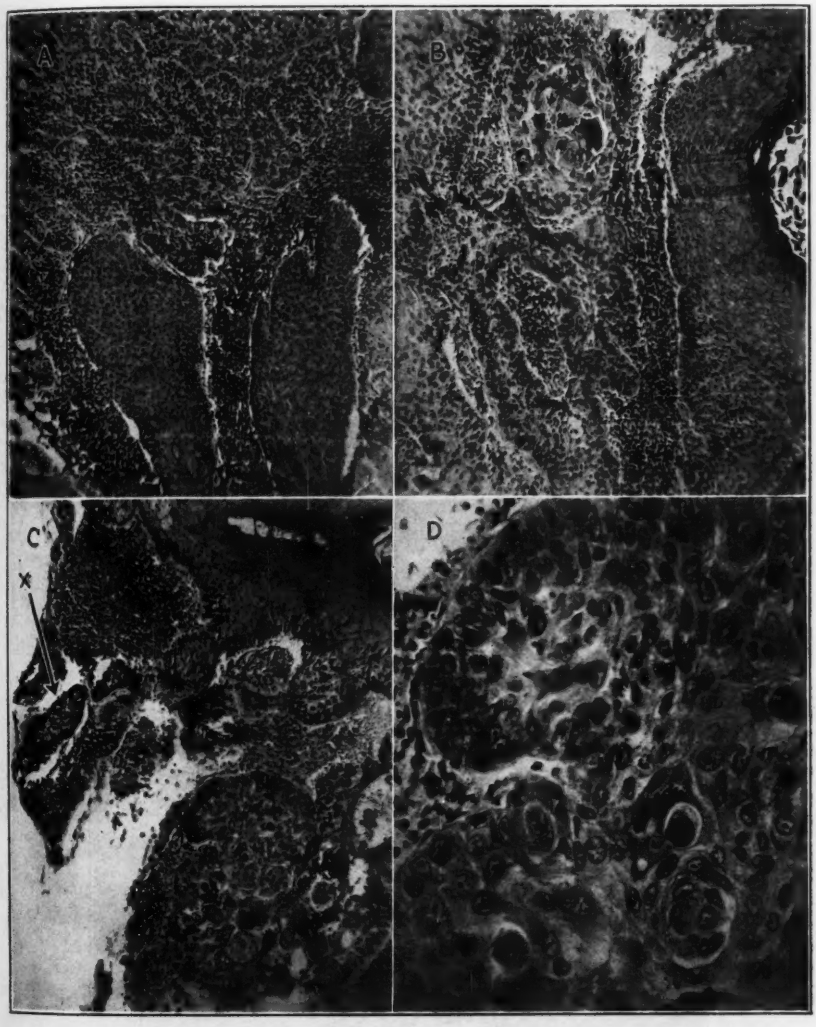

Fig. 2.—Transitional (intermediate) type. (Different magnifications of the same tumor.) *A*, low power view, of islands of penetrating squamous cell epithelioma with growth of the basal cells in columns. *B*, medium power view, showing an atypical follicle, a nest of anaplastic squamous cells and rows of basal cells. *C*, medium power view, of squamous cell epithelioma, with the nest of a typical adnexal tumor indicated by *X*. *D*, high power view of a portion of *C*.

instances again much is left to the imagination of the individual observer. Reexamination of these sections at different times often resulted in contradictory conclusions.

Fig. 3.—Transitional type. (Different magnifications of the same tumor.) *A*, low power view, showing atypical squamous cell growth from the surface, with an adnexal tumor in the depth. *B*, medium power view, of a portion of a sudoriparous adnexal type of tumor, with nests of squamous cells indicated by *X*.

III. *Mixed Type (Foot's "Basal Celled" Epithelioma).*—Of the mixed type we have found approximately 20 cases. The majority were of adnexal carcinomas, with areas of squamous epithelioma near the surface, which was invariably ulcerated. Such cases should not be considered to belong to a subgroup of adnexal carcinomas, since they represent a combination of stratified squamous cell epithelioma and adnexal carcinoma, the former probably arising secondarily in the margin of an ulcer. We have seen a considerable number of sections in which proliferative changes occurred in the epidermis overlying an adnexal tumor. Very often one observes pronounced acanthosis, development of excessive numbers of follicles and occasionally evidence of varying degrees of dedifferentiation in the epidermis.

Atypical proliferation of prickle cells and basal cells of the epidermis is not uncommon in adnexal tumors and does not justify the separation of such growths into a special type. Not knowing whether or not the superficial stratified squamous epithelial cell component may not simply be secondarily induced, and being uncertain of its true pathogenetic relation to the adnexal type of tumor, we have chosen to refer to this group of tumors as "mixed carcinoma" of the skin, rather than as the "basal celled" type.

IV. *Transitional Carcinomas.*—There is in this series a significant number of cases, however, in which it appears difficult, if not arbitrary, to decide on an irrevocable classification. It is not possible to determine accurately the frequency with which such transitional structures occur, since much depends on the willingness of the observer to admit the significance of variations from the classical picture. Some of these intermediary tumors were classified under different terms at different times of reexamination. These structures may be looked on as epidermoid cancers with basal cell features or as adnexal tumors with epidermoid features.

A. The epidermoid cancers with basal cell features are probably related to Darier and Ferrand's *épithéliome métatypique intermédiare.* They consist of nests of squamous epithelial cells, often decidedly anaplastic, with atypical keratinization. In some areas the bright red stained material can be identified as keratohyalin by its structural arrangement, and in other areas it resembles colloid material. The characteristic feature consists of a budding of the basal layer, which becomes more or less independent and arranges itself in a lacelike network of strands and columns, resembling the "ribbon-like" bands or festoons in some forms of the adnexal carcinomas. The cells, however, are larger, often cylindric and possess a light-stained cytoplasm, thus differing from ordinary so-called basal cells. Also, high power magnification often disclosed a greater degree of disparity. The resemblance to adnexal type of tumors is often evidenced by the expansile

growth with finger-like projections. The buds of "basal" cells not infrequently resemble tubules, and instances have been encountered in which true glandular structures were formed, showing lumens and partial lining by a double row of cells. Obvious coil glands, simulating

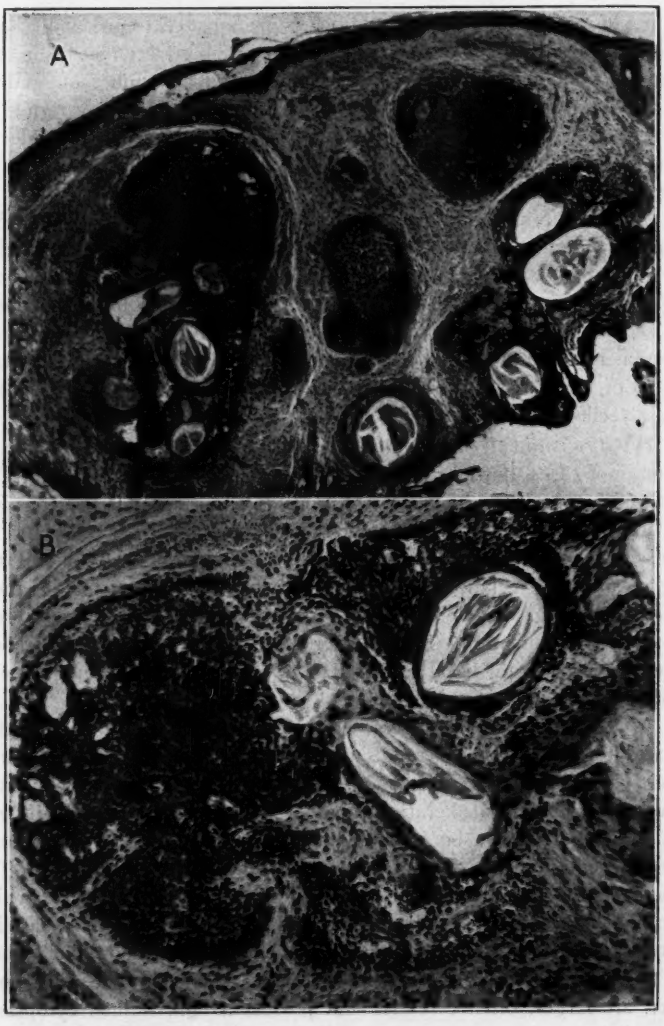

Fig. 4.—*A*, low power view of an adnexal carcinoma, pilar type proper, showing features characteristic of epithelioma adenoides cysticum. *B*, medium power view of the same tumor.

hair follicles, were seen to originate from nests of keratinizing anaplastic prickle cells.

B. Adnexal tumors with epidermoid features were characterized mainly by the appearance of atypical, laminated squamous cell elements in the center of primordial nests; occasionally, however, these prickle cells appeared in large nests as vacuolized elements resembling sebaceous cells. These cases were difficult to distinguish from those of true transitional tumors, and they may represent a malignant variety of the pilar type proper of adnexal carcinoma.

Transitional tumors, of which we have seen only a small number, show areas of both the adnexal and the epidermoid type of tumor blending into each other. Unless serial sections are made, it is difficult to determine whether or not such cases belong to what we have referred to as mixed tumor. Only those instances in which the complex tumor develops underneath an intact epidermis should be regarded as transitional.

COMMENT

The study of our material has impressed us with the frequency with which borderline neoplasms resist a clearcut classification as basal cell, basal-squamous cell or squamous cell epithelioma. Many cases had to be squeezed into the given "pigeon holes" by overemphasis of the quantitative preponderance of certain types of tumor cells or structures.

The greatest difficulty was encountered in the group of so-called basal-squamous cell epitheliomas characterized by the appearance of squamous epithelial elements in the center of basal cell nests. The histologic pattern, aside from this sign of differentiation, resembles too closely that of other basal cell tumors to warrant the segregation into a special oncologic entity. The term basal-squamous cell epithelioma implies that these basal cell tumors also possess characteristics of squamous cell epithelioma, an implication for which there is no support. The squamous epithelial cells are not seen to infiltrate independently in small groups or as isolated cells but always remain within their mantle of basal cells. The resemblance to abortive hair follicles, on the other hand, is apparent.

Montgomery [7] commented that the finding of normal adult follicles in a section showing no connection with the basal cell growth is not compatible with Foot's hypothesis. It is true in our own observation that numerous adult follicles are often seen in conjunction with the adnexal tumors. They are not always "pushed" aside, and, moreover,

7. Montgomery, H., and others: Atlas of Dermal Pathology, prepared [at the Army Institute of Pathology] by the Registry Committee on Dermal Pathology of the American Academy of Dermatology and Syphilology, Washington, D. C., Registry Press, 1947, pp. 48-49.

excess follicles are frequently encountered. This observation, however, in our opinion, does not affect the hypothesis of the origin of these tumors from adnexal primordia any more than does the occurrence of "multiple points of origin" in other types of epitheliomas.

We do not believe that the origin of these tumors can always be traced directly either to the basal cells or to an "initial mass between the basal layer and the rete" (Foot). Such an initial mass can occasionally be found in small tumors (particularly in the so-called "multiple flat epitheliomas") and may be interpreted as a peculiar type rather than as an early phase. Foot's illustration of the earliest change [8] seems to resemble very closely what Allen illustrated as the "Jadassohn" type.[9]

Although the initial point of origin cannot be determined in the majority of instances, we believe that Foot's concept, based largely on the ability of these tumors to differentiate, is logical and provides, as Arnold stated, "an integrated explanation of the basal cell carcinoma which accounts for its distribution, its variety of cellular patterns and its infiltrative—but never metastasizing—habits of growth." [10] The formation of stratified squamous cell centers resembling frustrate hair follicles, in nests of so-called basal cell epitheliomas, indicates a higher degree of differentiation.

The same holds true for "basal cell" tumors of the glandular type. An understanding of all the transitional varieties, including the many cases in which a distinction between the pilar and sudoriparous type is well-nigh impossible, is greatly enhanced by assuming their common origin from adnexal primordia. We have particular reference to the type of case in which the ribbon of so-called basal cells continues into a tubular-like structure, occasionally possessing a double lining, and to the primordial type resembling a solid hidradenoma. The occurrence of true combinations, which we observed, also supports this hypothesis.

We have not been able to follow Foot's classification of "basal-celled" tumor as a subgroup of adnexal carcinoma. We believe that the majority of such instances may be regarded as of mixed tumors in which squamous cell epithelioma is superimposed at the epidermal margin of an eroding ulcer.

There remains, however, a group of tumors which falls under neither of the previously discussed categories. We have classified these growths as "transitional" tumors, which are anaplastic but which show certain features of both epidermoid and adnexal tumors. With

8. Foot,[3] fig. 8.

9. Allen, A. C., in Anderson, W. A. D.: Pathology, St. Louis, C. V. Mosby Company, 1948, p. 1235, fig. 969.

10. Arnold, H. L., Jr.: Basal Cell Carcinoma of Sweat Gland Origin, Arch. Dermat. & Syph. **57**:1042 (June) 1948.

the acceptance of Foot's theory, some such neoplasms may justly be classified as primordial carcinomas of a high degree of malignancy.

SUMMARY

Clinical data concerning 1,257 patients with epitheliomas are presented. Half of all the lesions occurred in persons between 50 and 69 years of age. Men presented 53.7 per cent of the basal cell lesions and 67.2 per cent of the squamous cell variety. The occupational environment of 42.5 per cent of the patients was outdoors. Almost half of the patients waited from one to three years before seeking treatment. Of the series of lesions, 46.8 per cent had a surface diameter of more than 1 cm. Two thirds of the lesions occurring on the ear, jaw and hand were in men, whereas two thirds of the epitheliomas of the forehead, nasolabial area, chin, arm and leg appeared in women. While a majority of the lesions were of the basal cell variety, it did appear that, as the size of the lesions increased, the squamous cell type was found more frequently. Blonds had 84.4 per cent of all the lesions. The concept of an etiologic relationship between solar radiation and epithelioma is given additional support.

A histologic review of 968 epitheliomas is presented. Foot's concept of adnexal primordium as the focus of origin of so-called basal cell tumors is considered a satisfactory explanation of epitheliomas with transitional and mixed features.

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NODULAR VASCULITIS

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THE INCREASED interest and study of diseases of the blood vessels has brought to light many new syndromes which may be related or which may be separate diseases. The study of such diseases as disseminate lupus erythematosus, periarteritis nodosa, scleroderma, cranial (temporal) arteritis [1] and migrating phlebitis [2] has centered interest on many points of similarity in these diseases. A critical analysis of a group of cases observed in dermatologic practice in the light of our broader knowledge of vascular disease has stimulated this report. Allen [3] has discussed this condition as a nontuberculous form of erythema induratum, which it simulates closely; however, its frequency and its lack of tuberculous causation warrant its distinction from the usual erythema induratum both by name and by more general knowledge. The fact that we have been able to collect 6 cases during the past two years indicates that this is not a rare disease. A review of recent dermatologic literature discloses only an occasional reference to this condition. Montgomery, O'Leary and Barker [4] in their excellent article on nodular vascular diseases of the legs give a short discussion of the present problem, and Novy [5] suggests the underlying problem in the presentation of his case before the San Francisco Dermatological Society.

From the Department of Dermatology, University of Colorado School of Medicine, Dr. O. S. Philpott, professor, and from the practice of Drs. O. S. Philpott and A. R. Woodburne, Denver. Case 4 is from the clinical material of Dr. Joseph D. Friedland, Denver.

1. Horton, B. T.; Magath, T. B., and Brown, C. E.: An Undescribed Form of Arteritis of the Temporal Vessels, Proc. Staff Meet., Mayo Clin. **7**:700-701 (Dec. 7) 1932.

2. Barker, N. W.: Recurrent Idiopathic Thrombophlebitis of the Legs, M. Clin. North America **10**:597-599 (Sept.) 1934.

3. Allen, E. V.; Barker, N. W., and Hines, E. A.: Peripheral Vascular Diseases, Philadelphia, W. B. Saunders Company, 1946, pp. 487-490.

4. Montgomery, H.; O'Leary, P. A., and Barker, N. W.: Nodular Vascular Diseases of the Legs; Erythema Induratum and Allied Conditions, J. A. M. A. **128**:335-341 (June 2) 1945.

5. Novy, F. G., Jr.: Case for Diagnosis (Erythema Induratum?), Arch. Dermat. & Syph. **38**:997-998 (Dec.) 1938.

The general picture of nodular vasculitis is that of a healthy person between the ages of 13 and 60, with a history of recurrent, mildly painful and tender nodules of the anterior surface of the leg with occasional nodules of the thigh and upper extremities. The individual nodules persist for several months, and new lesions develop at intervals of one or two months. The disease lasts from a few months to several years, and nodules heal without atrophy, scarring or depression of the

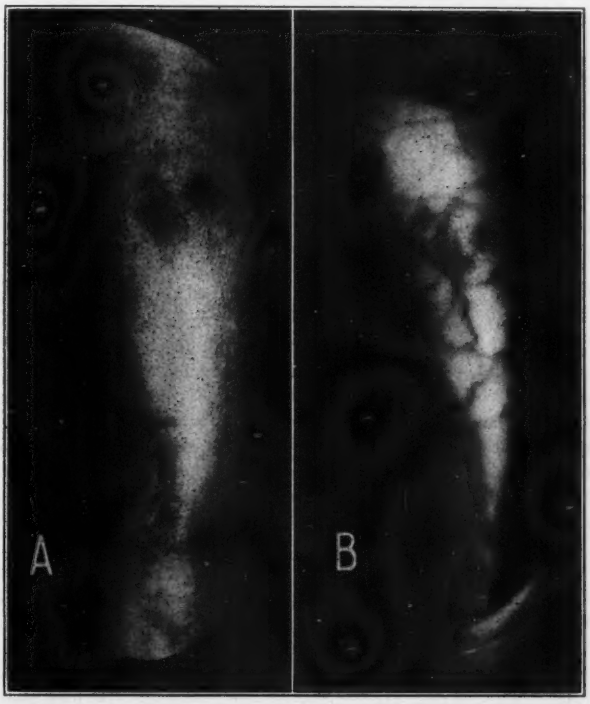

Fig. 1 (case 6).—*A*, typical clinical picture in nodular vasculitis; *B*, infra-red photography of the same lesion. Note the association of nodules and superficial vessels.

surface. New crops of lesions do not manifest a tendency to occur in cold weather. Changes in temperature and season do not seem to have an influence on lesions.

On physical examination the nodules resemble most closely those of erythema nodosum, being dusky red, mildly painful, moderately tender and usually seen on the anterior portion of the leg. These nodules do not, however, show capital points of extreme tenderness as is usual

in erythema nodosum. They manifest a definite tendency to group along the course of, and to include in themselves, superficial vessels; occasionally there are bean-sized to walnut-sized chains of nodules along vessels. The nodules heal without going through the bruise cycle so usual in erythema nodosum.

Histopathologic study discloses a panvasculitis with little or no change in the epidermis and with a diffuse lymphocytic infiltrate in the dermis, more pronounced about the vessels and coil glands and in the vessel walls. Aneurysmal pouches, necrosis or polymorphonuclear infiltration in the vessel walls is not apparent. The vessels have thickened walls with swollen endothelial cells. At the junction of the dermis and fat and in the fibrous trabeculae of the fat are large collections of lymphocytes and a few large mononuclear giant cells. Some collections of epithelioid cells are seen deep in the sections. Multinuclear giant cells may be seen in the deeper lesions, and a tuberculoid architecture is not unusual. There is no caseation or necrosis. Acid-fast or other organisms have not been found in any sections after prolonged study.

REPORT OF CASES

CASE 1.—D. U., a girl aged 18, a student, gave the history of painful nodules of the legs for the past two years. She had seldom been without one during this period, and an acute flare-up of the disease could be expected following tonsillitis. Her family and personal history was otherwise noncontributory. On physical examination she had, lateral to the midportion of the right tibia, a golf ball–sized nodular infiltrate, dusky red in color and moderately tender. A similar, smaller nodule just above and medial to the left femoral epiphysis was noted. She had cryptic and enlarged tonsils with pus in some crypts. Roentgenograms of the teeth revealed normal conditions. Examination of the blood and routine urinalyses gave normal results. Sedimentation rate of erythrocytes on four occasions was 4, 2, 2.5 and 3 mm. at the end of one hour (Cutler method). A complete tuberculosis survey, including roentgenogram of the chest, revealed normal conditions. The tuberculin test gave a 1 plus reading. The bleeding and the clotting time of the blood were normal. This patient has been observed over a period of eighteen months, during which many episodes occurred. Decided improvement occurred following tonsillectomy.

CASE 2.—R. H., a man aged 30, had lost the right leg as the result of the explosion of a land mine. Shortly after he was discharged from military service a painful nodule developed just above the internal malleolus of the left ankle. Although this had gradually subsided, new nodules had developed later along the course of the external saphenous vein, each new nodule usually being an inch or so above the previous one. When the patient was examined some eighteen months later he had a beadlike group of hickory nut–sized, dully inflammatory nodules on the lateral surface of the leg just below the knee and a group of three larger nodules medial to the knee in the lower portion of the thigh. Otherwise, physical examination revealed nothing unusual. Various laboratory observations were made. The sedimentation rate was 11.5 and 11 mm. per hour.

Results of a complete examination of the blood and urinalysis were within normal limits on several occasions; the Kahn test was negative, the tuberculin test gave a reading of 1 plus and roentgen examination of the chest revealed normal conditions. We were able to observe this patient through several episodes. Administration of penicillin in large doses for four weeks did not produce well defined change in the nodules. Use of sulfonamide compounds over a long period also proved ineffectual.

Fig. 2 (case 4).—Photomicrograph from deep dermis exhibits features similar to those in figure 5 but with more epithelioid cells (× 330).

Case 3.—G. B., a girl aged 14, had multiple, recurrent, painful nodules of twelve months' duration on the anterior portion of the legs and thighs. Five episodes of this condition were reported. Physical examination disclosed scattered nodules of the anterior surface of the legs, eight groups of two or three nodules and one or two single nodules, one single nodule of the lateral area of the left thigh and one of the left arm. Results of laboratory tests were not grossly

abnormal. A nodule removed from the lateral surface of the left leg for microscopic study illustrated the general features already described.

Case 4.—Mrs. E. I., aged 54, had had recurrent, painful nodules of the lower portion of the legs for five years. Examination revealed a bluish red nodule 2 by 3 cm. lateral to the left tibia opposite the junction of its lower and middle third. This nodule was deeply infiltrated, tender and apparently involuting. A more recent nodule was seen just below the right knee. Tissue was removed

Fig. 3 (case 6).—Gross appearance of characteristic nodular lesion (× 17.5).

from this area for study (figure 2). Laboratory studies gave normal results. There were no depressed areas, scars or atrophy indicating sites of previous lesions. A survey for tuberculosis which included roentgen examination of the chest and tuberculin tests disclosed normal conditions.

Case 5.—Mrs. E. T., aged 60, had multiple nodules in linear arrangement on the lower part of both legs and scattered groups on both thighs. This patient had an anal fistula and had experienced persistent diarrhea with recurrent

episodes of colitis accompanied with the development of nodules during the past eighteen months. Laboratory studies revealed no evidence of tuberculosis.

CASE 6.—Mrs. R. W. S., aged 38, had had recurrent, painful and tender nodules of the lower portion of the legs for eight months. These began as small, oval, tender areas. New lesions had developed periodically. The first group was at the junction of the lower and middle third of the left leg. This group consisted of four confluent nodules each about 1.5 cm. in diameter. During the

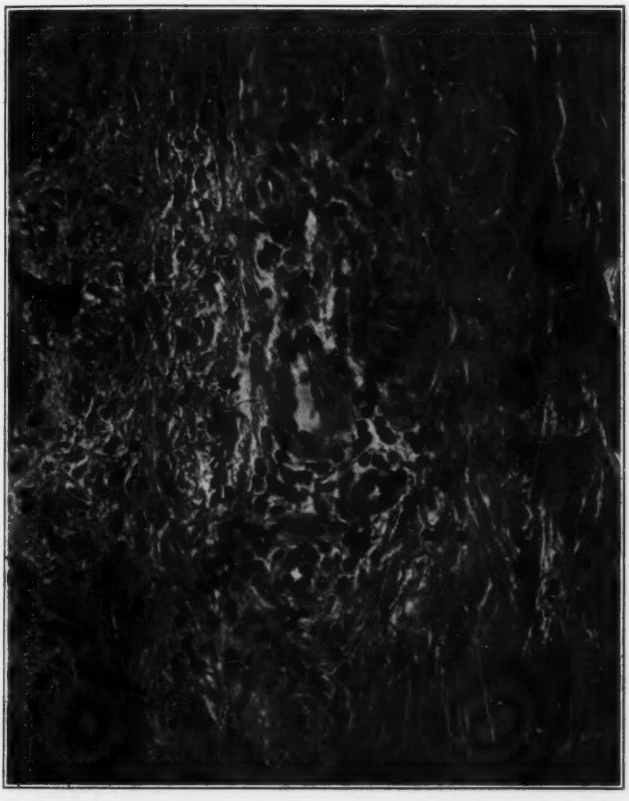

Fig. 4 (case 6).—Section from dermis of lesion in photomicrograph 3 exhibits characteristic diffuse lymphocytic infiltrate with focal collection about vessels in the center (× 330).

period of observation five or six other small nodules developed over the upper part of the left leg, with two small nodules on the anterior and lateral surface of the left leg. Two nodules were removed for microscopic examination (figs. 3, 4 and 5). Infra-red photography has shown the close association of these nodules with superficial vessels.

DIFFERENTIAL DIAGNOSIS

With previously noted positive points in physical and laboratory diagnosis kept in mind, we shall attempt to indicate points of differentiation between nodular vasculitis and other nodular lesions of the legs.

1. Lesions of erythema induratum (tuberculous type) are rarely painful and are only slightly tender, usually on the dorsal surface of the

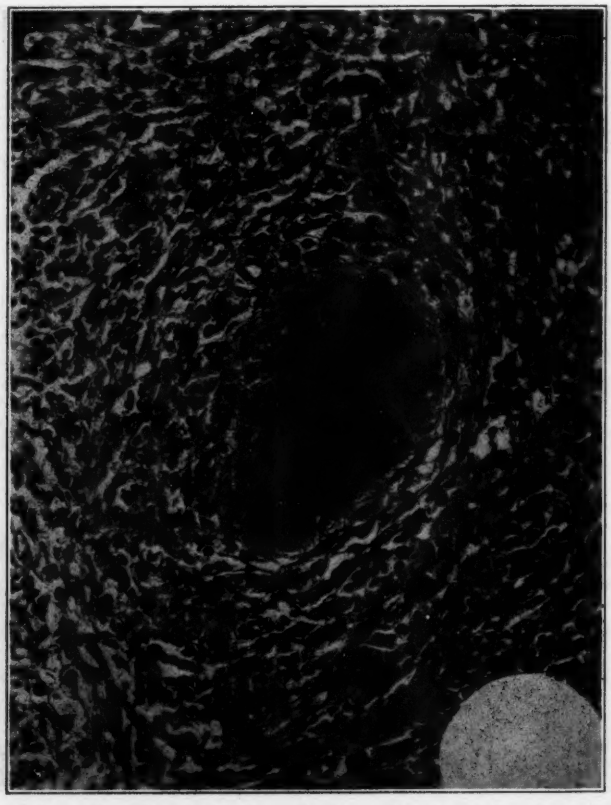

Fig. 5 (case 6).—Tissue taken lower in the section presented as figure 3 reveals a large collection of lymphocytes, occasional mononuclear cells, fibroblastic proliferation and a multinuclear giant cell (× 330).

calf. Ulceration is usual, and the inflammatory reaction is chronic. The tuberculin test gives positive results, and the microscopic architecture of the lesions is that of tuberculosis.

2. Lesions of erythema nodosum (*sui generis*) develop in a single crop. Although recurrences have been observed, they are not usual. The inflammatory reaction, pain and tenderness are acute and are usually

associated with an acute infection of the upper part of the respiratory tract or with rheumatic disease. Erythema nodosum is a self-limited disease, seldom of longer duration than six weeks, and it occurs usually in young girls. Individual lesions progress through the bruise cycle as they heal.

3. Erythema nodosum (symptomatic) is associated with the following conditions:

A. Tuberculosis. Nodules occur in young persons 10 to 18 years of age, associated with or following the primary tuberculous complex, with a negative response to the tuberculin test early in the disease and a positive result during or following the nodular episode.

B. Coccidiomycosis. The nodules develop a short time after an episode of pulmonary coccidioidomycosis ("valley fever"); the coccidioidin skin test becomes positive during or after the nodular episode.

C. Leprous erythema nodosum. Leprous erythema nodosum is found associated with the lepromatous form of leprosy, nearly always during periods of activity in which arthritic, neuritic and other evidence of the disease exhibit a definite exacerbation.

D. Diphtheria. Diphtheria may exhibit nodules simulating erythema nodosum associated with angina, membrane and positive throat culture.

E. Measles. Occasionally nodules of this type are seen with and following the typical eruption of measles.

F. Drugs. Drugs may produce lesions simulating those of erythema nodosum. Iodides and bromides in particular are responsible. Lesions due to drugs usually are more transitory, and a history of ingestion of the medicament can usually be obtained.

4. Thrombophlebitis follows the course of superficial veins and extends proximally along them. Tests of these veins reveal that they are occluded.

5. Tularemia nodules may be mistaken for those of erythema nodosum but are usually more acute and break down early; the presence of bacteria may be demonstrated, and agglutination tests become positive.

6. Nodular tertiary syphilis exhibits early ulceration, serpiginous outline, soft scarring with hyperpigmentation of borders and a positive response to serologic tests.

7. Chilblain is usually located over bony prominences or the achilles tendon; the peripheral circulation is easily influenced by changes in temperature, and there is a history of onset and exacerbation in cold weather.

8. Nodular nosuppurative panniculitis (Weber-Christian disease) is characterized by deeper nodules with recurrent crops associated with fever and healing with depressed areas of legs and thighs. The micro-

scopic study shows the pathologic process to be located in the subcutaneous adipose tissue. Healing occurs with replacement of fat by fibrous tissue and depression of the superimposed dermis and epidermis. It may be that nodular vasculitis is closely related to this syndrome. However, since the inflammatory reaction in nodular vasculitis is in the dermis, healing that occurs by fibrosis does not result in depression of superior tissues.

9. Periarteritis nodosa manifests as a rule smaller nodules, more evidence of involvement of internal organs, and a microscopic display of aneurysmal dilatation of vessels, polymorphonuclear infiltration and necrosis of vessel walls. Periarteritis nodosa has been reported as an allergic response to various agents, occasionally to the sulfonamide compounds.

10. Sarcoid as a rule exhibits fewer nodules and less inflammatory reaction; the nodules are usually painless. Microscopic examination will exclude this condition.

11. Sarcoma is usually a single tumor or appears in a single group. This disease displays no inflammation and has a characteristic microscopic picture.

TREATMENT

Treatment in nodular vasculitis has been as a rule unsatisfactory. Prolonged rest in bed with elevation of the legs and the application of warm or cool compresses have been the most generally helpful measures. Removal of foci of infection has seemed to be of importance in other instances. In case 1 improvement was rapid after the removal of infected tonsils; in case 6 the patient responded well to the extraction of an abscessed molar. Web or elastic support to the lower part of the legs has been helpful in some instances. Allen [8] has obtained good results with the use of a streptococcus vaccine in ascending doses below the level productive of reactions. The antibiotic agents have seemed to be of help at first but have never produced permanent improvement. Large doses of salicylates have made the patients more comfortable and have seemed to aid involution of the lesions in several cases.

SUMMARY

Six cases of a nodular, moderately painful and tender eruption of the legs are reported. The differential diagnosis and pathologic features of the eruption are discussed, and some observations on etiology and treatment are made. It is our opinion that nodular vasculitis is a definite clinical and pathologic syndrome which is not rare. It may be related to periarteritis nodosa or nodular nonsuppurative panniculitis, but it should be recognized and separated from other more generally recognized nodular disturbances of the legs and thighs.

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THERAPY OF PSYCHOSOMATIC DERMATOSES

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TO CLASSIFY a dermatosis among the psychosomatic disorders of the skin is not always difficult, but treatment may prove to be a real problem. A study of the accompanying chart [1] may aid in the decision as to the best method of management in a given case. The diseases listed (delusion of parasitosis, phobias [cancer, syphilis], neurotic excoriations, dermatitis factitia, psychogenic pruritis, neurodermatitis [atopy], trichotillomania, hyperhidrosis, urticaria, pompholyx, rosacea, lichen planus, seborrhea, psoriasis, alopecia, vitiligo, canities, acne vulgaris, herpes and warts) range from the purely psychic to those in which psychic factors are questionable.

Disorders of the skin that are purely psychic will usually require psychiatric treatment to the exclusion of the dermatologist once a diagnosis is made, whereas those in which psychic factors predominate may primarily require treatment by a psychiatrist with perhaps considerable aid from the dermatologist. As the shading in the chart lightens, there is a corresponding lessening in the degree to which the patient may be mentally ill, with the result that treatment by the dermatologist becomes increasingly important. It may be helpful to discuss individually some of the diseases listed in the illustration.

Wilson and Miller,[2] to whom I am indebted for separating out cases designated as delusion of parasitosis from the phobias, point out that the psychiatrist occasionally—the dermatologist rarely—succeeds in curing the delusion. They recommend modern electric shock and insulin shock therapy as employed by psychiatrists as most likely to improve the prognosis considerably in certain groups.

Levine [3] believes that some phobias of disease, notably syphilis and cancer, are deep-seated and persuasive and may be unmodifiable or at

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1. Psychosomatic Medicine in Relation to Dermatology, read before the Southern Medical Association, Miami, Florida, Oct. 27, 1946.

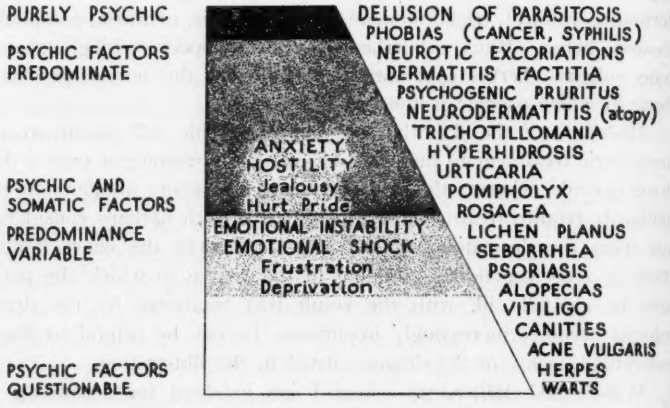
2. Wilson, J., and Miller, H. E.: A Delusion of Parasitosis (Acarophobia), Arch. Dermat. & Syph. **54**:39 (July) 1946.

3. Levine, M.: Psychotherapy in Medical Practice, New York, The Macmillan Company, 1942; revised 1945.

best modifiable only with deep-going methods of psychotherapy. Other cases are mild, and in such cases an impressive examination followed by an unambiguous statement of physical normality may be sufficient for cure or adequate amelioration of the condition.

For patients with self-inflicted lesions such as neurotic excoriations psychiatric aid is usually necessary, but with self-inflicted lesions produced for a definite purpose such as getting attention or arousing sympathy, unraveling the underlying cause may suffice to prevent further demonstration.

In the study of neurodermatitis made by Walsh and Kierland [4] at the Mayo Clinic, conscientious psychotherapy was administered to 15 patients. In 3 patients with pronounced depressive reaction a series of electric shock treatments was also given. With 1 exception (a



Stereoscopic diagram of the psyche and soma in dermatology

patient in whom there was failure because of a language difficulty) improvement in the emotional disorders was paralleled by a complete or nearly complete clearing of the dermatologic reaction; the improvement endured for the period of observation in all patients whose dermatologic reaction first appeared in adult life.

Psychogenic pruritus may also be a problem for the psychiatrist. In a physician aged 50 who was treated at the Temple University Hospital for an intolerable pruritus for which no somatic cause could be found, electric shock therapy brought about a complete and lasting cure after the patient failed to respond to local therapy, diet, sedatives and psychiatric consultation.

4. Walsh, M. N., and Kierland, R. R.: Psychotherapy in the Treatment of Neurodermatitis, Proc. Staff Meet., Mayo Clin. **22**:578 (Dec. 10) 1947.

Psychiatric help may also be required for trichotillomania, which is often regarded by the psychiatrist as a form of masturbation, although proper approach by the dermatologist may result in cure. Other types of hair loss such a alopecia areata and general thinning of the hair, which may at times ocur after nervous shock or prolonged emotional disturbances, usually respond to dermatologic therapy. The same applies to the intermittent type of hyperhidrosis, although at times this may be a true psychiatric problem.

In the intermediate group of diseases in which psychic and somatic factors vary in their predominance, the emotional factor is seldom deep and can usually be managed by the dermatologist. For example, psoriasis, which is considered incurable, will often clear completely with freedom from the disease for variable and often prolonged periods of time. If the possibility of this relief is explained to the patient instead of using the commoner approach and stating that "psoriasis is incurable," improvement or even temporary "cure" may be obtained rather than loss of faith in ethical medicine and resultant compromise with advertised patent remedies.

Vitiligo, canities and warts have been placed at the bottom of the list, for there is little or no proof that psychic factors have any real causative effect. Whether warts respond to psychotherapy is in my opinion still controversial, because they are known to be due to a virus and virus infections will usually disappear spontaneously in time.

Success or failure in the treatment of psychosomatic disorders is often dependent on the first consultation between the patient and the physician. The physician who has no sympathy with nervous manifestations and takes a hostile attitude or manifests a frank disinterest in this phase of his patient's disease will usually fail in his therapeutic efforts. Vice versa, the quick assumption that nervous factors are solely to blame and failure to make a thorough search for physical causes may also result in therapeutic failure.

When psychotherapy is introduced in the treatment of cutaneous conditions, efforts to treat the skin itself are being relaxed and a new element is introduced for the discovery of precipitating factors; this procedure doubtless often makes a contribution toward correction of the underlying exhaustion. One does not then rely so much on drugs and other treatments applied to the skin, but thoughts of physician and patient are turned toward the mental irritations which may be finding their way to the skin either through the phenomenon of conversion involving symbolization or through well known pathways of the autonomic nervous system to pervert circulation, glandular activity or both, or to cause trophic changes.

If the physician looks sympathetically and helpfully for nervousness as an etiologic factor, the patient will generally help and with each visit will bring added information or clues as to the relation of emotional

distress and symptoms. The psychiatrist has found that time to allow for reorientation in thinking is important and that a speedy solution to emotional problems is infrequent. Hence, there is no reason to be discouraged with psychotherapy because it does not remove the patient's symptoms immediately. Dermatology and psychiatry may seem to be widely separated specialties, but they have in common a few acute manifestations of symptoms and many chronic ones which yield slowly to therapy.

When the dermatologist has definitely or with reasonable assurance made up his mind that he is dealing with a psychosis, it becomes necessary to make the patient accept the idea that a psychiatrist should be consulted. This is by no means easy, and the following steps are suggested: (1) inform the family rather than the patient of your diagnosis; (2) consult with the family regarding the possible reaction of the patient when told of such a diagnosis; (3) get the opinion of the family or some member of the family as to whether they or you should make the disclosure. If the problem of referral to a psychiatrist is not handled carefully, dissatisfaction on the part of both patient and family is apt to result, with complete loss of confidence in the dermatologist and eventual therapeutic failure.